OCTOBER 1978 • VOL. 188, NO. 4
ISSN 0003-4932 • ANSUA5

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CUK-H01453-21-P024763

ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

21

September and October numbers contain papers delivered at
THE 98th ANNUAL SESSION
of the
AMERICAN SURGICAL ASSOCIATION
Dallas, Texas, April 26-28, 1978

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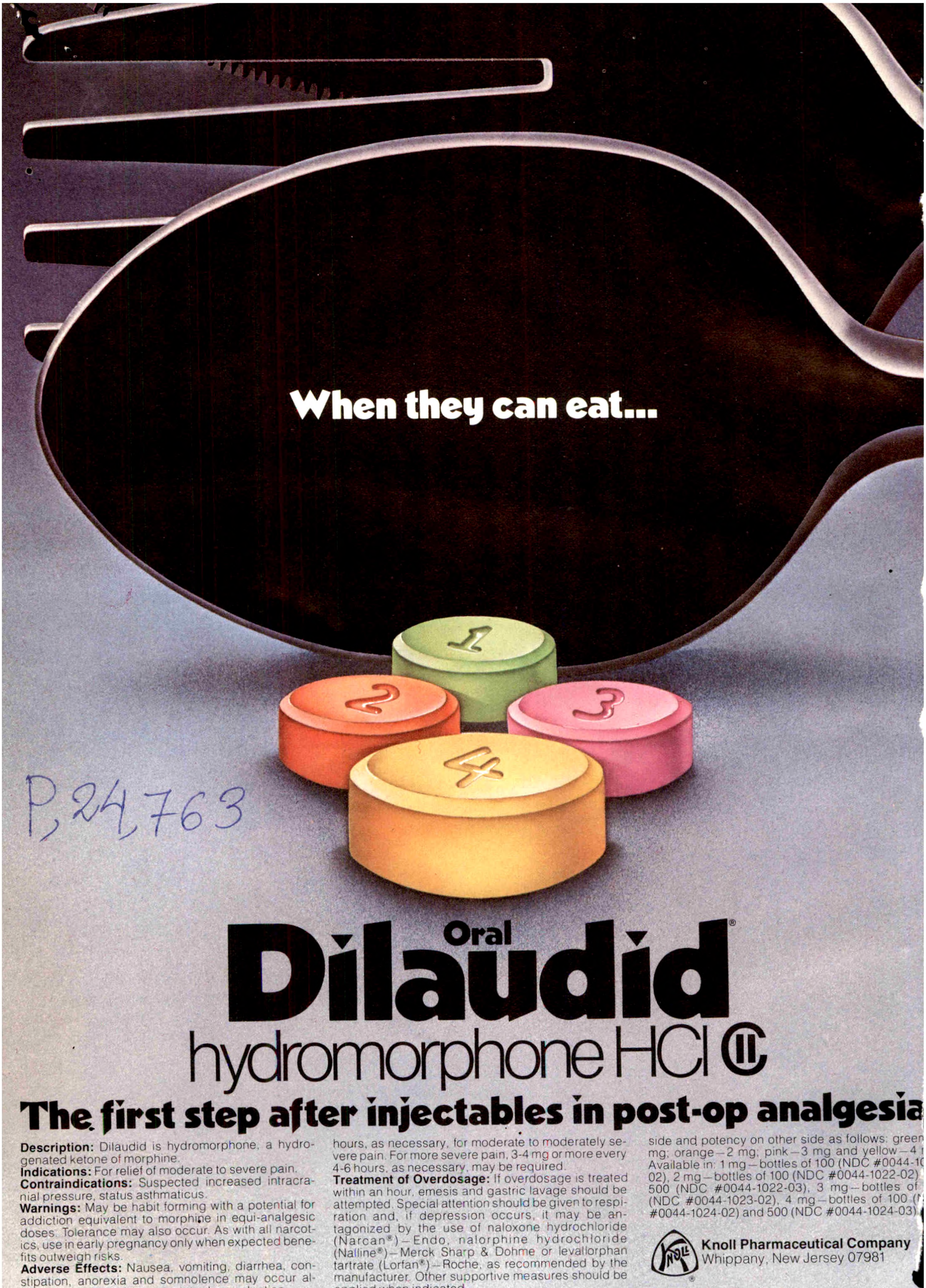

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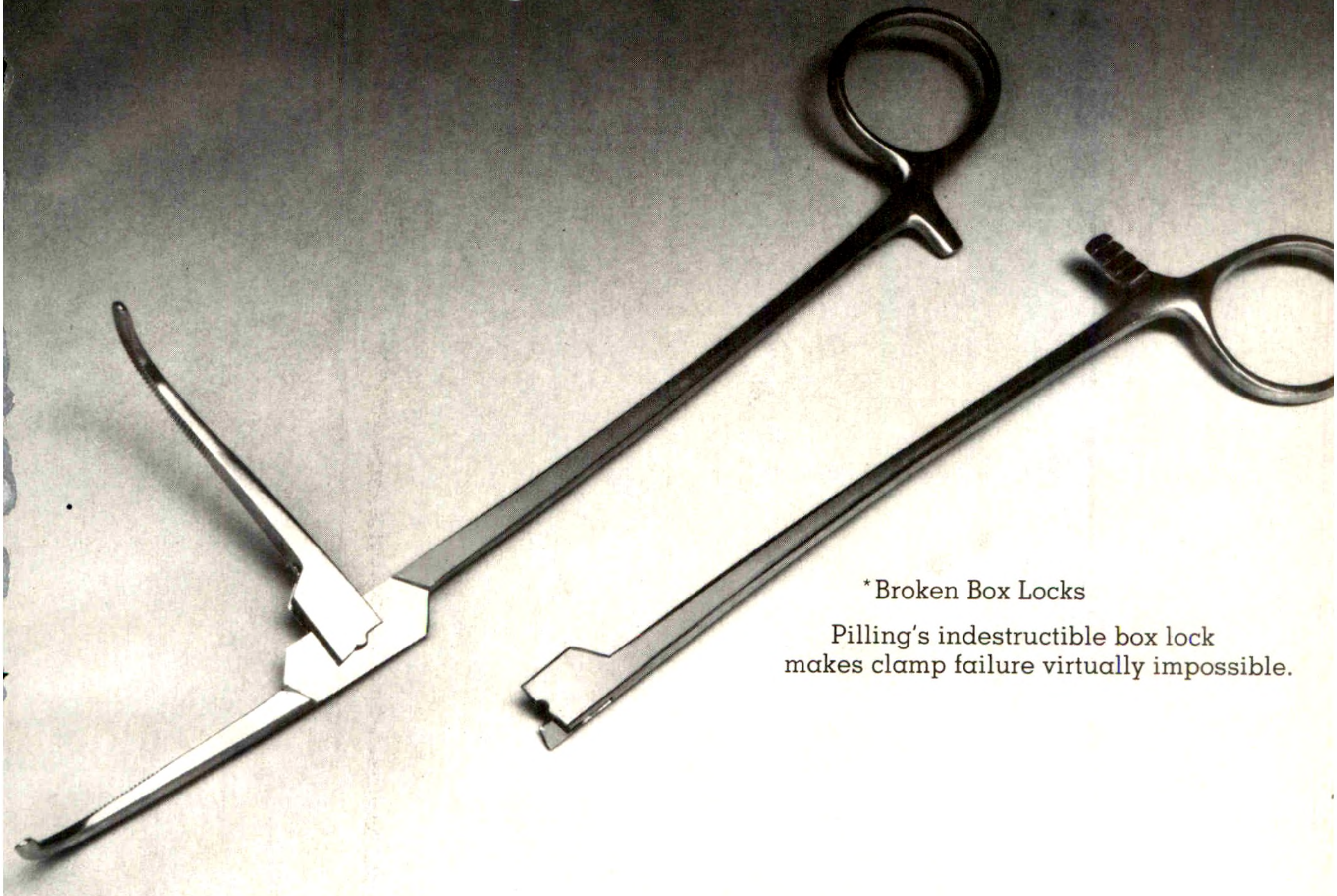

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*As shown in animal studies; TVC—True Vomiting Center, CTZ—Chemoreceptor Trigger Zone.

**Please see brief summary for detailed information concerning potential adverse reactions.

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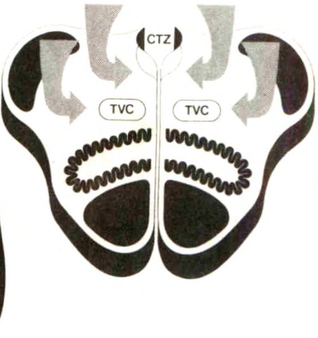

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Torecan® (thiethylperazine)
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Contraindications: Severe CNS depression, comatose states, and in patients who have demonstrated a hypersensitivity to phenothiazines (e.g., blood dyscrasias, jaundice). Because severe hypotension has been reported after the intravenous administration of phenothiazines, this route of administration is contraindicated. The drug is contraindicated in pregnancy.

Warnings: Phenothiazines are capable of potentiating CNS depressants as well as atropine and phosphorous insecticides. The drug may impair mental and/or physical ability required in the performance of potentially hazardous tasks such as driving a car or operating machinery. *Postoperative Nausea and Vomiting.* When used to control postoperative nausea and vomiting in patients undergoing elective surgical procedures, restlessness and postoperative CNS depression during anesthesia recovery may occur. Possible postoperative complications of a severe degree of any of the known reactions of this class of drug must be considered. Postural hypotension may occur after an initial injection, rarely with the tablet or suppository. Do not use with epinephrine in the treatment of drug-induced hypotension as phenothiazines may induce a reversed epinephrine effect. The most suitable vasoconstrictor agents are levarterenol and phenylephrine. The use of Torecan has not been studied following intracardiac and intracranial surgery. Not recommended for use in children under 12 years of age, or in nursing mothers since safety and efficacy have not been established.

Precautions: Convulsions and abnormal movements such as extrapyramidal symptoms have occurred. The varied extrapyramidal symptom complex is more likely to occur in young adults and children. Extrapyramidal effects must be treated by reduction of dosage or cessation of medication. For treatment of nausea and/or vomiting associated with anesthesia and surgery, the drug should be administered by deep intramuscular injection at or shortly before the termination of anesthesia.

Adverse Reactions: CNS: convulsions, extrapyramidal symptoms such as dystonia, torticollis, oculogyric crisis, akathisia and gait disturbances, occasional cases of dizziness, headache, fever and restlessness have been reported. Drowsiness may occur initially on injection but is usually alleviated by a reduction in dosage. Dryness of the mouth and nose, blurred vision, tinnitus; sialorrhea and altered gustatory sensation. Peripheral edema of the arms, hands and face. Cholestatic jaundice; cerebral vascular spasm and trigeminal neuralgia have been reported occasionally. The following have occurred with phenothiazine derivatives and should be considered: agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia, pancytopenia, eosinophilia, leukocytosis; miosis, obstipation, anorexia, paralytic ileus; erythema, exfoliative dermatitis and contact dermatitis; jaundice, biliary stasis. Hypotension, rarely leading to cardiac arrest; ECG changes. Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia, some of which have persisted for several months or years especially in patients of advanced age with brain damage. Menstrual irregularities, altered libido, gynecomastia, weight gain; false positive pregnancy tests. Urinary retention, incontinence; fever, laryngeal edema and angioneurotic edema, asthm Hyperpyrexia, behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. ECG changes. While there is no evidence that ECG changes are in any way precursors of any significant disturbance of cardiac rhythm, sudden and unexpected deaths apparently due to cardiac arrest have been reported in a few instances in hospitalized psychotic patients previously showing characteristic ECG changes. A peculiar skin-eye syndrome, which is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea, has also been recognized as a side effect following long-term treatment. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. *Drug Interactions:* Phenothiazines are capable of potentiating CNS depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorous insecticides. The drug may induce a reversed epinephrine effect on occasion.

For complete details, please see full prescribing information.

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Second-class postage paid at Philadelphia, Pa., and at additional mailing offices. Published monthly. Subscription $27.00 per United States. Resident Rate (U.S. only) $19.00. All other countries $37.00. Single issue $5.00. All prices include postage.

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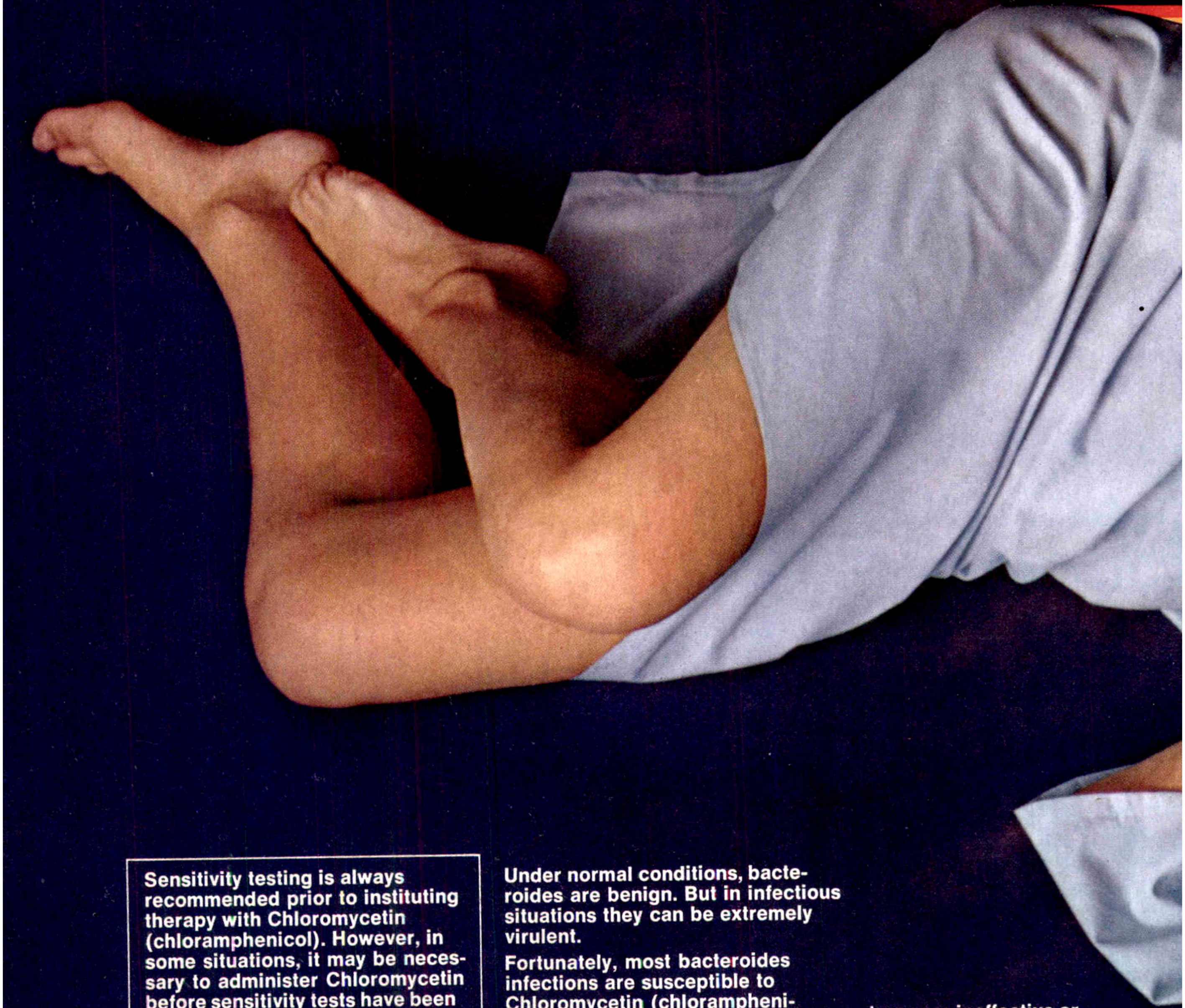
Bacteroides

may be implicated in a number of clinical situations, including . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena



Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

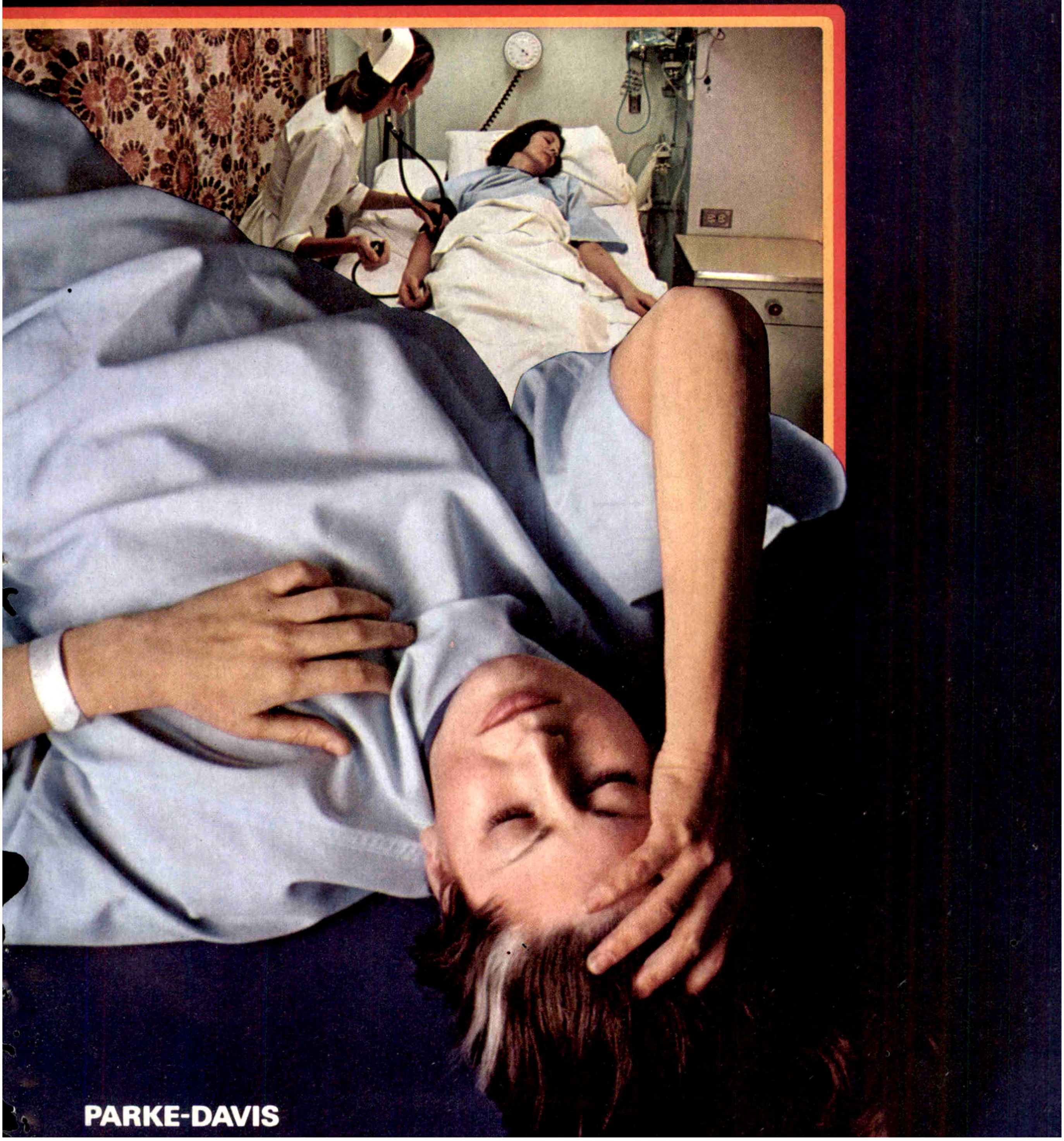
Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated.

But when bacteroides are implicated, Chloromycetin (chloramphenicol) therapy may well be the conservative course. For, in such situations, the benefits-to-risk ra with Chloromycetin is very favorab

See next page for full prescribing information.

Bacteroides...
often an indication for
CHLOROMYCETIN®
(chloramphenicol) Sodium Succinate



PARKE-DAVIS

Prescribing information—Chloromycetin (chloramphenicol) Sodium Succinate
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for*, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**
   It is not recommended for the routine treatment of the typhoid carrier state.
2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.
   a) *Salmonella* species
   b) *H influenzae*, specifically meningeal infections
   c) Rickettsia
   d) Lymphogranuloma-psittacosis group
   e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
c) The symptoms appeared in the following order:
   (1) abdominal distension with or without emesis;
   (2) progressive pallid cyanosis;
   (3) vasomotor collapse, frequently accompanied by irregular respiration;
   (4) death within a few hours of onset of these symptoms.
d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants
(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 2 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the bloo should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinat is supplied as a dried powder in Steri-Vials (rubber diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per millilite (1 g/10 ml). Available in packages of 10 vials.

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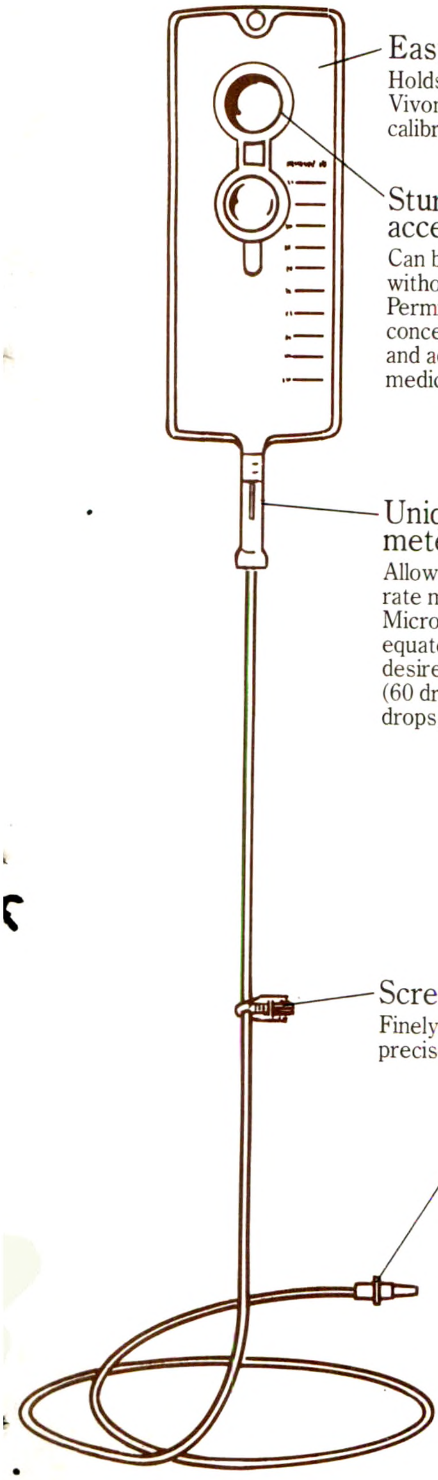

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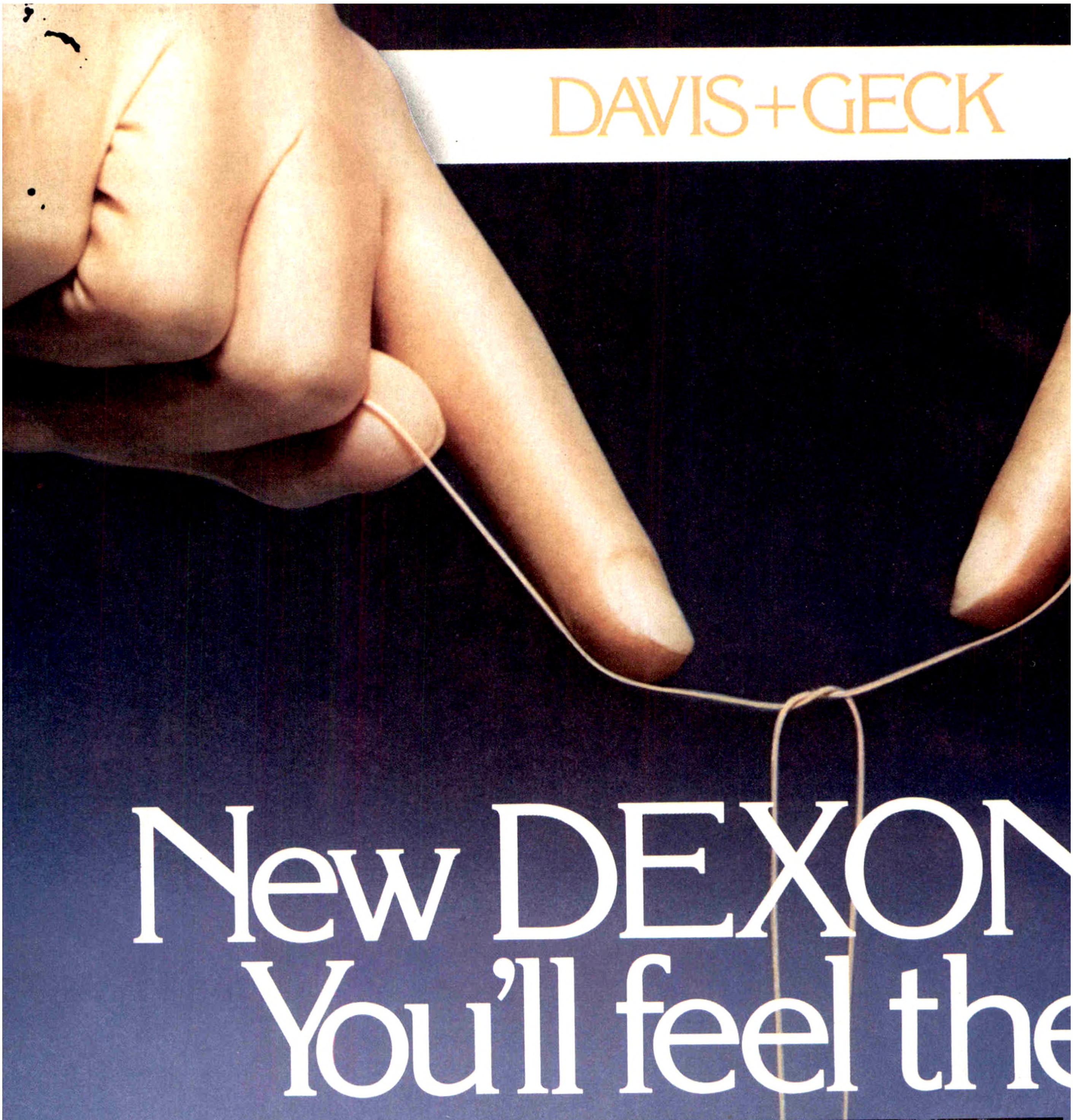

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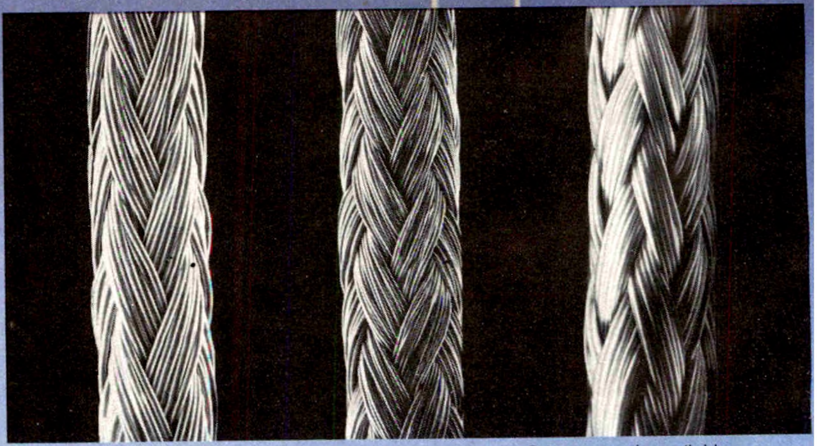

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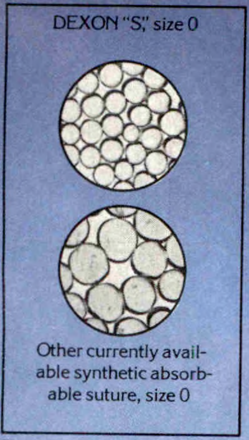

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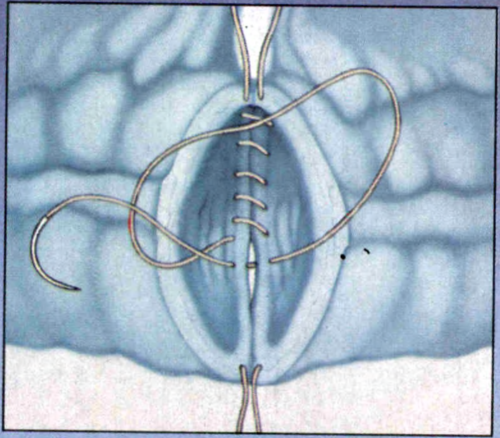

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Complete Product Information

DESCRIPTION DEXON "S" *polyglycolic acid* Suture-Synthetic, Absorbable, USP is a homopolymer of glycolic acid, constructed of filaments finer than in original DEXON to provide optimal handling properties. The sutures are sterile, inert, noncollagenous, nonantigenic, nonpyrogenic, flexible, and braided. They are colored green to enhance visibility in tissue and are also available undyed, with a natural beige color. They are uniform in size and tensile strength, but are smaller in diameter than other Absorbable Surgical Sutures of equivalent tensile strength.

ACTIONS When DEXON "S" is placed in tissues a minimal tissue reaction occurs, which is followed by a microscopic layer of fibrous connective tissue which grows into the suture material.

Absorption studies in animals show DEXON "S" to be equivalent to original DEXON. Studies in rabbits revealed minimal absorption at 7 to 15 days, significant absorption at 30 days, and maximum resorption after 60 to 90 days.

Tensile strength, not being a function of the absorption rate, may vary from tissue to tissue, depending in part on the rate of hydrolysis. The early tensile strength of DEXON "S" is reported to be greater than that of comparable chromic catgut. In animal studies (subcutaneous tissue in rats) it has been shown that at two weeks post-implantation approximately 55% of the original tensile strength of DEXON "S" remains, while at three weeks approximately 20% of its original strength is retained.

INDICATIONS DEXON "S" sutures are indicated whenever absorbable sutures and ligatures are employed.

CONTRAINDICATIONS DEXON "S" is contraindicated where extended approximation of tissues under strain must be maintained.

WARNINGS The safe use of this suture in neural tissue and in cardiovascular surgery has not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize. Discard opened, unused sutures.

PRECAUTIONS Acceptable surgical practice should be followed with respect to drainage and closure of infected wounds.

Knots with DEXON "S" *polyglycolic acid* Suture must be properly placed to be secure. Therefore, place first throw in precise position for final knot, using a double loop; tie second throw square using horizontal tension; additional throws may be used as desired.

Skin sutures which remain in place for periods of longer than seven days may cause localized topical irritation and the extended portion of suture may be snipped off after five to seven days, as indicated.

ADVERSE REACTIONS Those reactions that have been reported include tissue reaction or inflammation, fibrous or granulation tissue, wound separation and bleeding, and accumulation of fluid around subcuticular stitches.

DOSAGE AND ADMINISTRATION Use as required.

HOW SUPPLIED Suture sizes 8-0 through 2 dyed green and 7-0 through 2 natural beige. Supplied in cut lengths or ligating reels, non-needled or affixed to the various DAVIS + GECK ATRAUMATIC® needles or D-TACH® *removable needles* USP in one and three dozen packages.

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*Ross, S. *et al.*: JAMA *229*: 1075 (Aug. 19) 1974.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Prostaphlin® (oxacillin sodium)
Capsule and Oral Solution (11) PROSTAPHLIN 9/11/75

For complete information, consult Official Package Circular.

Indications: Although the principal indication for oxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to oxacillin sodium should be performed.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of oxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to oxacillin sodium, the physician is advised to continue therapy with a drug other than oxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Oxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins

staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A previous hypersensitivity reaction to any penicillin is a contraindication.

Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

The possibility of bacterial and/or fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Experience in premature and newborn infants is limited. Caution should be exercised in administration of the drug to such patients and frequent evaluation of organ

Safety for use in pregnancy has not been establishe

Adverse Reactions: The hypersensitivity reactions reported are skin rashes, urticaria, serum sickness and anaphylactic reactions. Oral lesions such as glossitis a stomatitis have been reported. Fever, eosinophilia, oral and rectal moniliasis have also been reported. Hemoly anemia, transient neutropenia with evidence of granulocytopenia or thrombocytopenia, neuropathy, and nephrotoxicity (oliguria, albuminuria, hematuria, pyuria, and/ cylindruria) are infrequent and usually associated with high doses of parenteral penicillin.

In some newborns and infants receiving high doses oxacillin sodium (150 to 175 mg./Kg./day), transient hematuria, albuminuria, and azotemia have been encountered. Although the causal relationship is not entirely clear, infants and newborns treated with high doses of the drug should be observed closely for signs of renal impairment.

One patient developed granulocytopenia while receiving intravenous oxacillin sodium and vancomycin. The blood count returned to normal after both drugs were discontinued. Another patient was reported to have leukopenia during intravenous therapy with oxacillin sodium. These counts were made while the patient was moribund. Thrombophlebitis has occurred in a small pe centage of patients after intravenous therapy.

Usual Oral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Administer on empty stomach for maximum absorption.

Usual Parenteral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Children weighing 40 Kg. or more should receive the adult dose.

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"Intraperitoneal kanamycin therapy is strongly advocated for any patient with peritonitis." —DiVicenti, F.C., and Cohn, I., Jr.: Am. Journ. Surg. 111:1, pages 147-153, (June) 1965.

"In peritonitis, intraperitoneal administration of kanamycin can be recommended..." —Pissiotis, C.A., et al.: Surg. Gynecol. Obstet. 134:995 (June) 1972.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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(kanamycin sulfate injection)

(13) 2/28/78

For complete information, consult Official Package Circular.

WARNING:

The major toxic effect of parenterally administered kanamycin sulfate is its action on the auditory portion of the eighth nerve. High frequency deafness usually occurs first and can be detected by audiometric testing. Tinnitus or vertigo may occur and are evidence of vestibular injury and impending bilateral irreversible deafness.

In patients with impaired kidney function, the risk of severe ototoxic reactions and permanent deafness is sharply increased. In such cases, the daily dosage should be reduced and the interval between doses lengthened. If there is evidence of progressive renal dysfunction (increasing NPN, BUN, creatinine or oliguria) during therapy, audiometric tests are advised and discontinuation of the drug should be considered.

Older patients and patients receiving a total dose of more than 15 Gm. of kanamycin sulfate should be carefully observed for signs of eighth nerve damage.

Infants and children generally tolerate the drug well; and when the recommended precautions are followed, the incidence of toxic reactions is low.

Neuromuscular paralysis with respiratory depression may occur when kanamycin sulfate is administered intraperitoneally concomitantly with anesthesia and muscle-relaxing drugs. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug.

The concurrent systemic use of other ototoxic and/or nephrotoxic drugs, particularly streptomycin, polymyxin B, polymyxin E (colistin), neomycin, gentamicin, and viomycin should be avoided.

The administration of kanamycin sulfate and rapid acting diuretic agents, e.g. ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, and mannitol (particularly when the diuretic is given intravenously) may cause irreversible deafness. Concurrent use of these agents should be avoided. (See "Adverse Reactions".)

Usage in Pregnancy

Safety of this drug in human pregnancy has not been established.

CONTRAINDICATIONS:

A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other potentially ototoxic agents may be a contraindication if effective, alternative therapy is available.

THIS DRUG IS **NOT** INDICATED IN LONG-TERM THERAPY (e.g. Tuberculosis) BECAUSE OF THE OTOTOXIC HAZARD WITH EXTENDED ADMINISTRATION.

WARNING:

See "Warning" box above.

PRECAUTIONS:

Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occurs, discontinue therapy. Mycotic or bacterial superinfection may occur.

ADVERSE REACTIONS:

Nephrotoxicity – albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity – see box warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

DOSAGE AND ADMINISTRATION:

The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult total daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gm.

The intravenous route is used only if intramuscular administration is not feasible. The 500 mg. dose is added to the 200 ml. of sterile diluent and administered 60 to 80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

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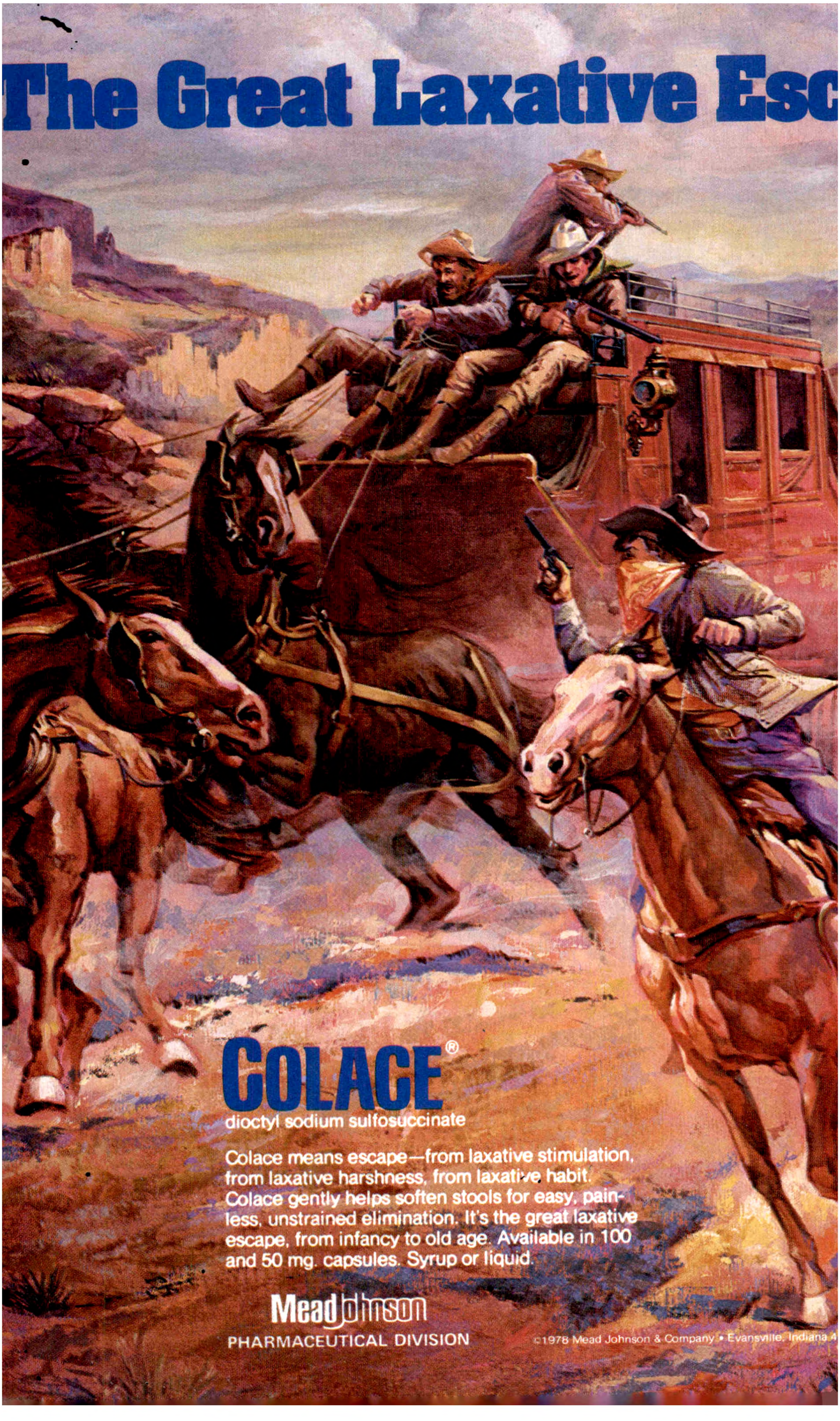

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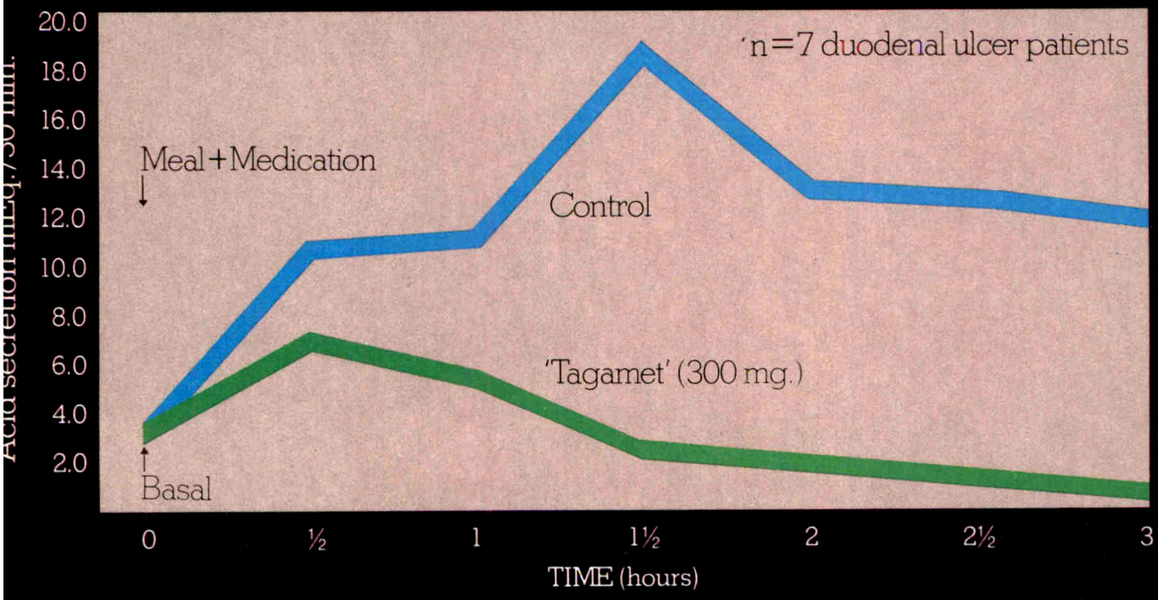
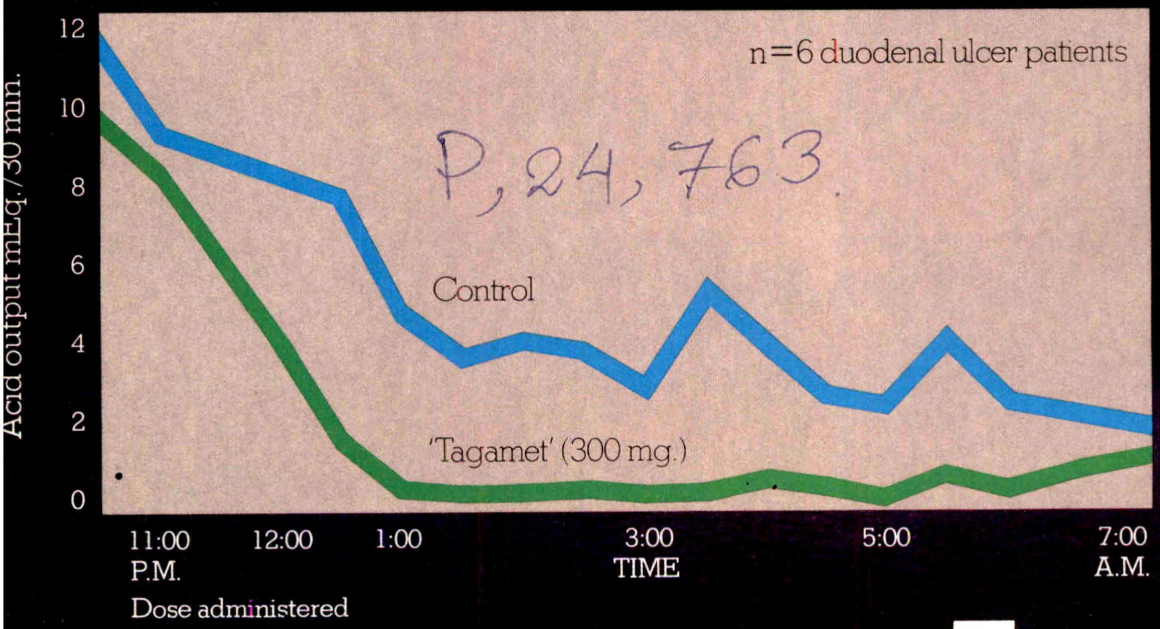


Tagamet' significantly ($p < 0.001$) suppressed nocturnal acid secretion all night.[2]



P, 24, 763.

Tagamet
brand of
cimetidine

References

1. Richardson, C.T., et al.: Gastroenterology 71 (1): 19-23 (July) 1976.
2. Longstreth, G.F., et al.: New England J. Med. 294:801-804 (Apr.) 1976.

The dramatic acid-suppressing effect of 'Tagamet' produces important patient benefits where it matters most:

- Rapid ulcer healing
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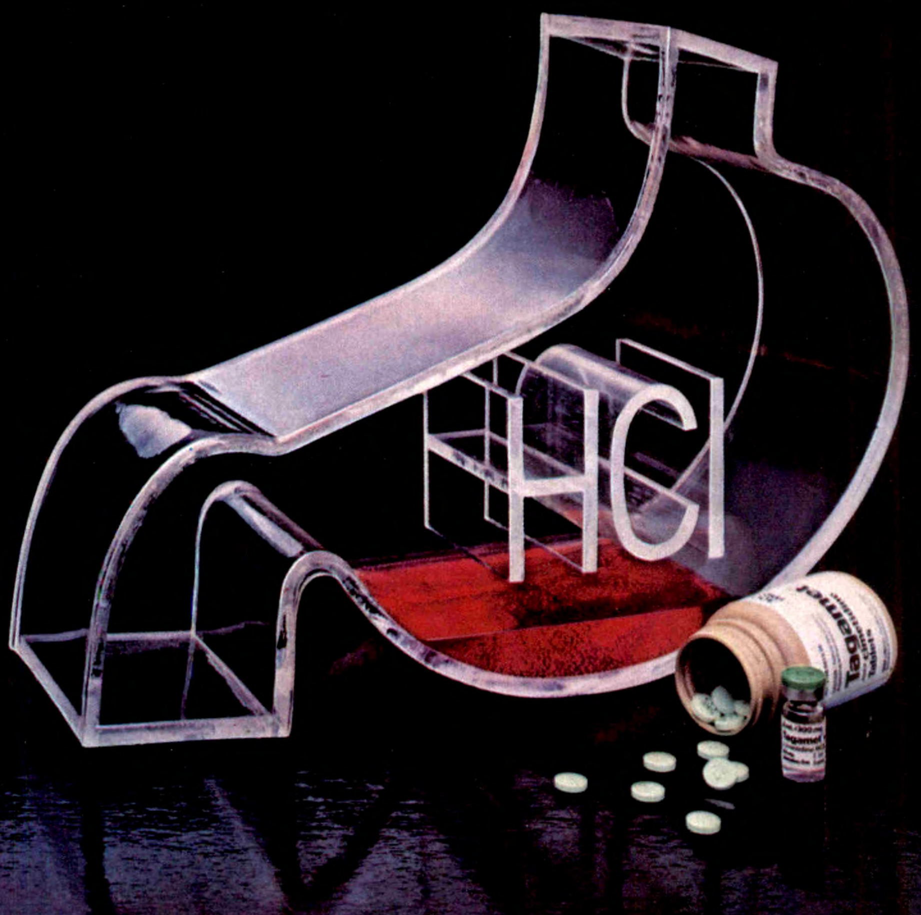

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Tagamet®
brand of

SK&F LAB CO.

Tagamet®

brand of Tablets, 300 mg. Injection, 300 mg./2 ml.

cimetidine

Effective duodenal ulcer therapy through significant gastric acid suppression.

In *Duodenal Ulcer,* the recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been demonstrated by endoscopic examination.

In *Pathological Hypersecretory Disorders,* the dosage is also 300 mg. four times a day, with meals and at bedtime. In some patients it may be necessary to administer 'Tagamet' 300 mg. doses more frequently (not to exceed 2400 mg. per day) and continue as long as clinically indicated.

Concomitant antacids should be given as needed for relief of pain.

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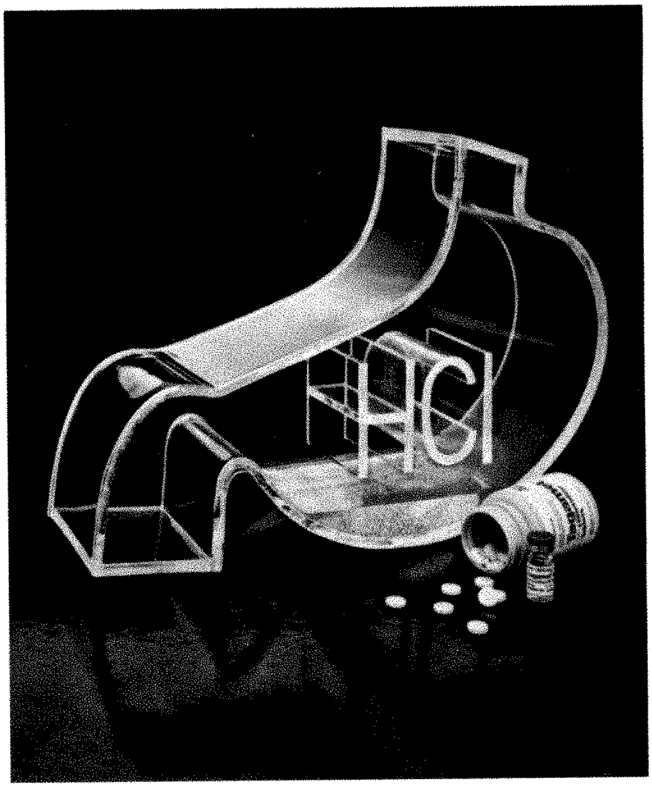
Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.



Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

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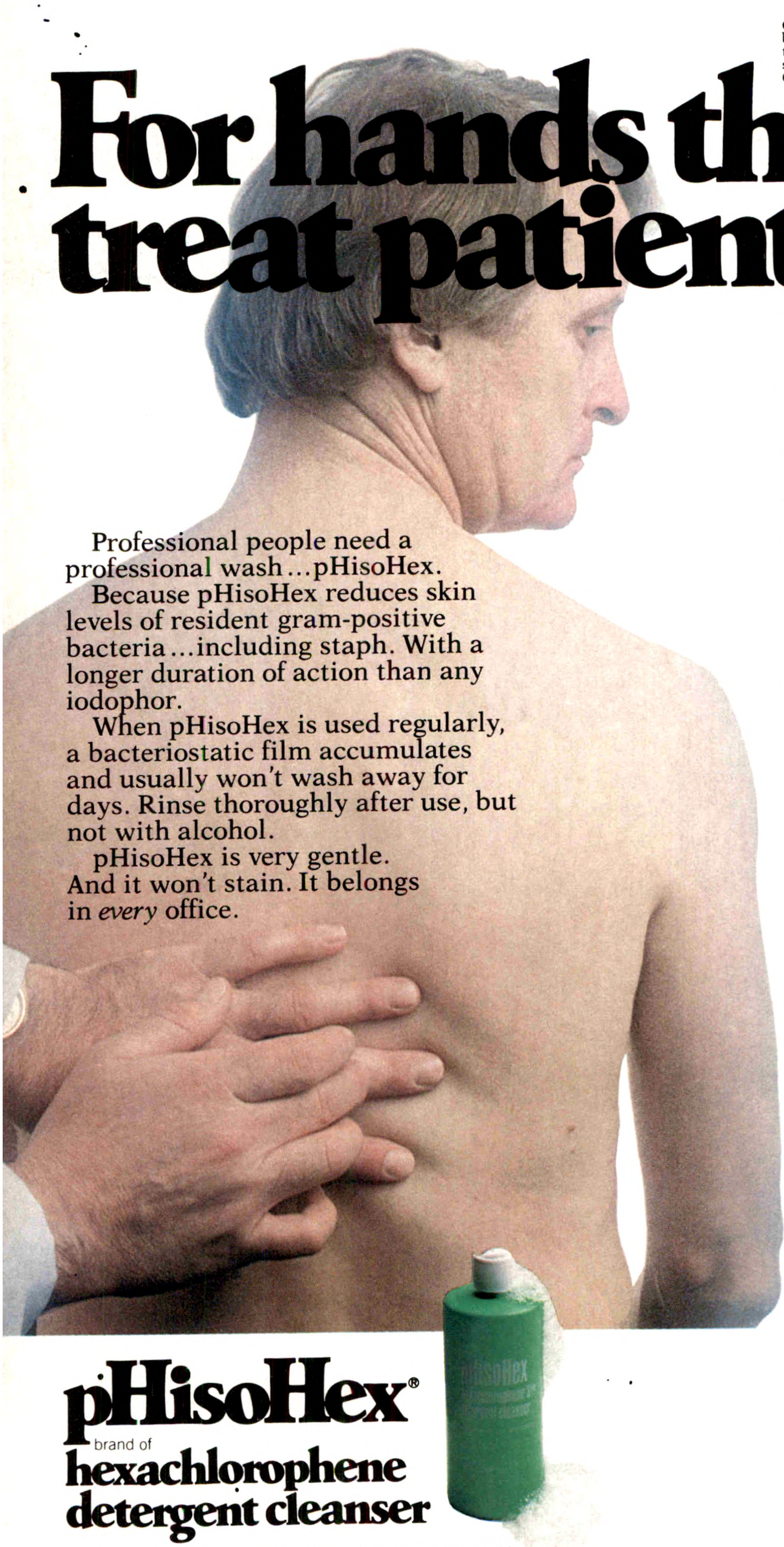

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It should not be used routinely for prophylactic total body bathing.

It should not be used as a vaginal pack or tampon, or on any mucous membranes.

pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

WARNINGS: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Rapid absorption of hexachlorophene may occur with resultant toxic blood levels, when preparations containing hexachlorophene are applied to skin lesions such as ichthyosis congenita, the dermatitis of Letterer-Siwe's syndrome, or other generalized dermatological conditions. Application to burns has also produced neurotoxicity and death.

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pHisoHex is intended for **external use only.** If swallowed, pHisoHex is harmful, especially to infants and children. **pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.**

PRECAUTION: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly with water.

ADVERSE REACTIONS: Adverse reactions to pHisoHex may include dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

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If patients are seen early, the stomach should be evacuated by emesis or gastric lavage. Olive oil or vegetable oil (60 ml or 2 fl oz) may then be given to delay absorption of hexachlorophene, followed by a saline cathartic to hasten removal. Treatment is symptomatic and supportive; intravenous fluids (5% dextrose in physiologic saline solution) may be given for dehydration. Any other electrolyte derangement should be corrected. If marked hypotension occurs, vasopressor therapy is indicated. Use of opiates may be considered if gastrointestinal symptoms (cramping, diarrhea) are severe. Scheduled medical or surgical procedures should be postponed until the patient's condition has been evaluated and stabilized.

HOW SUPPLIED: pHisoHex is available in unbreakable plastic squeeze bottles of 5 oz (refillable) and 1 pt, and in plastic bottles of 1 gal.

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ANNALS OF SURGERY

Vol. 188 October 1978 No. 4

Effect of Selective Proximal Vagotomy and Truncal Vagotomy on Gastric Acid and Serum Gastrin Responses to a Meal in Duodenal Ulcer Patients

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To assess the effectiveness of selective proximal vagotomy (SPV) in reducing the acid response to food, we have compared pre- and postoperative gastric acid and serum gastrin responses to a meal in 11 duodenal ulcer patients with intractable pain treated by SPV, with those of seven ulcer patients with gastric outlet obstruction treated by truncal vagotomy and drainage (TV + D). Acid secretion was measured by an intragastric titration method which measures acid response to food within the stomach (5% amino acid meal) adjusted to various pH levels (5.5, 2.5, and 1.5). Studies were performed before and two to six weeks after operation. The preoperative intragastric acid output (IGAO) was about 50% of maximal acid response to Histalog. The mean preoperative IGAO at pH 5.5 for 11 SPV patients was 17.4 ± 3.1 mEq/hour; this was decreased by 72% to 4.3 ± 1.1 mEq/hour after operation. The mean IGAO at pH 5.5 in nine patients treated by TV + D was 21.6 ± 3.4 mEq/hour; this was decreased by 67% to 7.3 ± 2.1 mEq/hour. Gastrin levels were significantly higher in postop than in preop SPV patients even though pH values were constant. Gastrin levels were higher in postop TV + D patients than in postop SPV patients. This study demonstrates that acid reduction achieved by SPV is reliable and at least comparable with that achieved by truncal vagotomy. Postoperative elevation of gastrin in the SPV patients suggests that the vagus may release a humoral inhibitor of gastrin release from the gastric fundus; there may also be a further direct vagal inhibitor of antral gastrin release.

IN THE ELECTIVE surgical treatment of duodenal ulcer, the procedure of selective vagal denervation of the gastric fundus (which we will refer to as selective proximal vagotomy) approaches the theoretical ideal, in that it appears to be an effective treatment for the ulcer with little risk of mortality or serious complications.[1,9,13,15,21] The procedure offers the promise of curtailing acid secretion without the need for resection or drainage. Compared with other acid-reducing operations, selective proximal vagotomy appears to have distinct advantages, especially in the low risk of mortality, as well as in the near elimination of postoperative dumping and diarrhea.[29] The questionable aspect of the procedure is whether acid secretory levels can reliably be reduced to the point that ulcers will remain healed. There are occasional reports of high rates of ulcer recurrence[18] and high incidences (80–90%) of positive Hollander tests.[12]

We have recently compared acid and endocrine responses to an amino acid meal in normal duodenal ulcer subjects.[30] The technique appears to offer an excellent means of reproducibly evaluating secretory

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Presented at the Annual Meeting of the American Surgical Association, April 26–28, 1978, Dallas, Texas.

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* Visiting Scientist. Parent Institution: Institute of Physiology, Medical Academy, Karkow, Poland.

Supported by grants from the National Institutes of Health (AM 15241) and General Clinical Research Centers Branch, DHEW Grant (RR 00073), and by a grant from the John A. Hartford Foundation, Inc.

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and endocrine responses to a nearly physiologic stimulus. In the present study, we have compared the gastric acid and serum gastrin responses to such a meal, before and after operation, in duodenal ulcer patients treated by selective proximal vagotomy with those of patients treated by truncal vagotomy and gastroenterostomy.

Studies on the relationship of the vagus to antral gastrin have suggested that the vagus may suppress, as well as stimulate, gastrin release.[2,3,22] The present studies have allowed us to study further the vagal control of gastrin release. The results suggest that the vagus may *inhibit* gastrin release by more than one route.

Materials and Methods

We have done a prospective study of 20 patients with duodenal ulcer disease who were admitted or transferred to the Surgical Service of The University of Texas Medical Branch Hospital over a 14-month period. Eleven of these patients were candidates for operation because of intractable pain (two had bled recently as well). One of these eleven was a woman; 10 were men, and their ages ranged from 23 to 59 years. The diagnosis of duodenal ulcer was confirmed by upper gastrointestinal barium x-ray studies and by fiberoptic gastroduodenoscopy. The duration of the patients' symptoms ranged from 6 months to 10 years. Five patients had previously bled from the upper gastrointestinal tract and two had had a perforated ulcer. All patients underwent elective selective proximal vagotomy; none of the patients in the group were operated on as an emergency and none had signs or symptoms of gastric outlet obstruction.

We will compare the results of acid secretory and serum gastrin measurements in the above 11 patients treated by selective proximal vagotomy with those of nine patients operated on for symptoms of gastric outlet obstruction. Of the remaining nine, five were women and four were men, and their ages ranged from 22 to 63. Their symptoms ranged in duration from 2 months to 12 years. Two patients had bled previously and one patient had undergone previous perforation. All patients had clear symptoms and signs of chronic gastric outlet obstruction. In every case, this was confirmed by upper gastrointestinal barium roentgenography, gastroscopy, and saline load testing.[5]

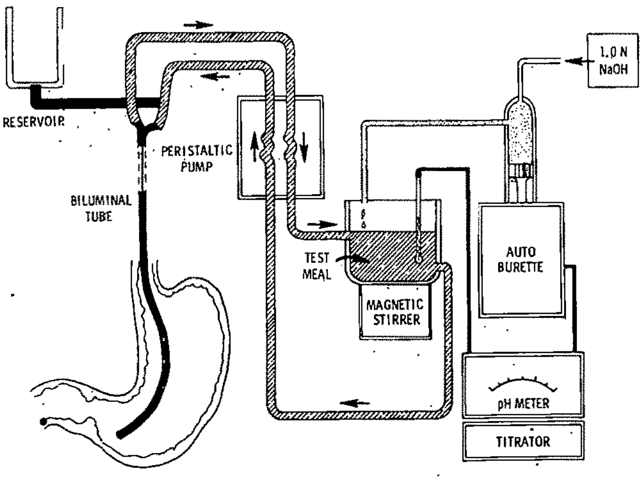

FIG. 1. Schema of intragastric titration technique (reproduced with permission from Thompson JC and Swierczek JS, Annals of Surgery 186:541–548, 1977).

In addition to the roentgenographic and endoscopic examination, each patient also had a standard gastric analysis, in which the basal acid output and the maximal acid output to Histalog (betazole, 1.5 mg/kg) was determined. Each patient underwent measurement of acid secretion by a technique of intragastric titration described previously.[30] This method, a modification of the technique of Fordtran and Walsh,[4] will be described briefly for clarity (Fig. 1); it allows continuous measurement of gastric secretory responses to the intragastric instillation of an amino acid meal. For the present study, we have used 400 ml of a 5% amino acid solution (caseine hydrolysate + 1% DL-tryptophan, Stuart Pharmaceuticals, Wilmington, Delaware) adjusted to 300 mosm. Continuous mixing of the test meal substance was achieved with a Harvard® peristaltic pump which continuously circulated the liquid from the stomach via a biluminal nasogastric tube to an 800 ml titration chamber. A reservoir, which functioned both as a barostat and as a safety valve, was connected to the reinfusion tube and was maintained at 20 cm above the supine patient.

The intragastric pH was maintained at any selected level by means of a pH-stat assembly consisting of a glass calomel electrode inserted into the titration chamber and connected to a pH meter, titrator and autoburette which delivered 1.0 N NaOH. Acid output was calculated from the amount of NaOH required to maintain the preselected pH.

In the intragastric titration study, patients underwent measurement of two basal specimens of 30 minutes each, after which the amino acid solution was introduced at pH 5.5 for one hour. The solution was then removed, the pH was adjusted to 2.5 and the solution was returned for one hour. The process was repeated, the pH adjusted to 1.5 and the solution was returned for one more hour. Blood samples were obtained for measurement of gastrin by radioimmunoassay[10] before the introduction of the test meal and at 30, 60, and 90 minutes after introduction of the meal.

Acid secretory values are available on all patients at all periods, but some gastrin samples were lost in processing so that complete gastrin data are available on nine patients who underwent selective proximal vagotomy and six patients who underwent truncal vagotomy.

The technique for selective proximal vagotomy has been described.[6,14] We have been careful to heed the admonition of Hallenbeck and colleagues[8] to elevate the vagal trunks carefully from the esophagus and to divide all branches from the vagi to the intraabdominal portion of the esophagus. Additionally, we have carefully denervated the area of the angle of His and have searched for all nerves going to the left of the esophagus to the fundus. All patients were operated upon by one surgeon (JCT).

The second group of patients underwent standard truncal vagotomy with creation of an anterior gastrojejunostomy placed immediately proximal to the pylorus.

Intragastric titration studies were repeated at two to six weeks after operation in all patients. We have late intragastric titration studies (6–12 months postoperative) in four patients.

Informed consent for participation in the study was obtained from each person. The protocol for the entire study was approved by the Research Committee for the Protection of Human Subjects of The University of Texas Medical Branch.

Results are expressed as the mean plus or minus one standard error. Except where noted, the Student's t-test was used to analyze the data for statistical significance of differences between means. Differences with a *p* value of less than 0.05 were considered significant. Where indicated, data were analyzed by analysis of variance.[25]

Results

• There were no deaths and no serious complications in the 20 patients operated upon. In the short time that they have been followed postoperatively, all patients have had excellent clinical results. The patients operated upon by selective proximal vagotomy have been entirely asymptomatic. Two of the patients who underwent truncal vagotomy plus gastroenterostomy for gastric outlet obstruction had difficulty with gastric emptying in the early postoperative period. Normal emptying resumed spontaneously in both.

Good stimulation of acid secretion was achieved by intragastric titration at pH 5.5. Much smaller amounts of acid were made at pH 2.5 and 1.5. At pH 5.5, the maximal acid output (MAO) in 11 selective proximal vagotomy (SPV) patients was 17.4 ± 3.1 mEq/hour. This was 49% of the MAO to Histalog (35.5 ± 5.7 mEq/hour) in the same patients (Fig. 2). The intragastric secretory output at pH 5.5 was 21.6 ± 3.4 in nine patients prior to truncal vagotomy plus drainage (TV + D). This was 55% of the Histalog MAO (43.8 ± 4.7 mEq/hour).

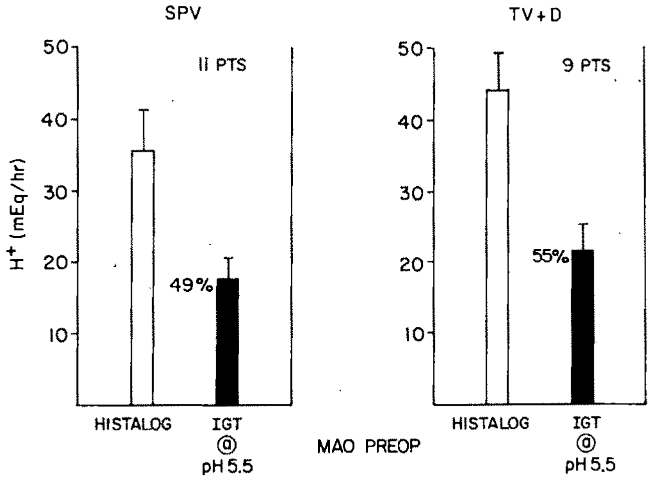

FIG. 2. Comparisons of preoperative maximal acid output (MAO) in 11 patients later treated by selective proximal vagotomy (SPV) and nine patients later treated by truncal vagotomy and drainage (TV + D) in studies using Histalog and intragastric titration at pH 5.5.

Significant reductions in acid output measured by intragastric titration at pH 5.5 were achieved after both selective proximal vagotomy and truncal vagotomy plus drainage (Fig. 3). Preoperative acid output at pH 5.5 ranged from 4.6 to 36.3 mEq/hour in the SPV patients. After operation, secretory values ranged from 0.1 to 11.1 mEq/hour. Preoperative acid secretory levels at pH 5.5 ranged from 4.3 to 37.0 mEq/hour in nine patients who were operated upon by truncal vagotomy plus drainage. After operation, these patients secreted between 0.7–15.9 mEq/hour. The average preoperative secretory output at pH 5.5 was 17.4 ± 3.1 mEq/hour in the SPV patients and 21.6 ± 3.4 mEq/hour in the obstructed patients who later under-

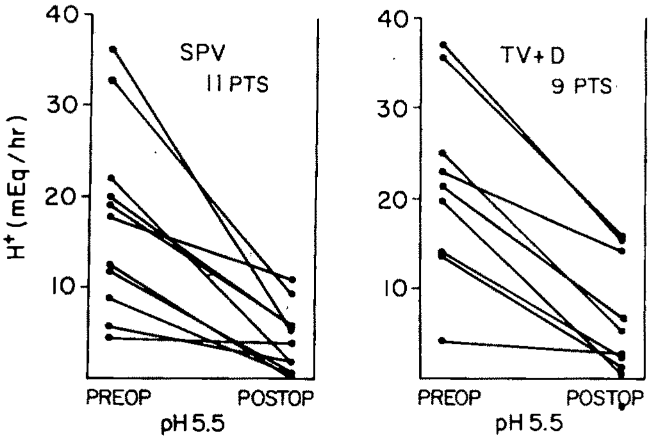

FIG. 3. Individual preoperative and postoperative acid secretory responses as measured by intragastric titration at pH 5.5 in 11 patients treated by selective proximal vagotomy (SPV) and nine patients treated by truncal vagotomy plus drainage (TV + D).

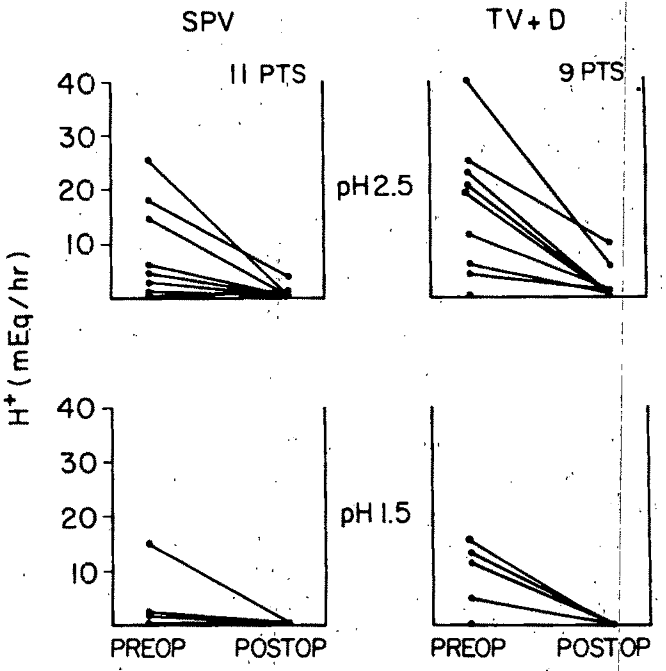

FIG. 5. Individual pre- and postoperative acid secretory responses measured by intragastric titration at pH 2.5 and pH 1.5 in patients treated by SPV and TV + D. At the lower pH levels, several patients had little or no acid output so that the points are superimposed at the bottom of the graph.

went truncal vagotomy (Fig. 4). After operation, the SPV patients had an average acid output of 4.3 ± 1.1 mEq/hour for a mean reduction of 72%; after truncal vagotomy and drainage, the average acid output was 7.3 ± 2.1 mEq/hour for an average acid reduction of 67%.

The degree of acid reduction in patients studied by intragastric titration at pH 2.5 and 1.5 was similar in the two operative procedures, but slightly greater with SPV (Fig. 5). The majority of patients made negligible amounts of acid pre- and postoperatively at the lowest pH level.

We obtained later (6–12 months) repeat studies of intragastric secretory measurements in four SPV patients. The average preoperative acid output at pH 5.5 was 17.1 ± 1.8 mEq/hour, which fell to 5.9 ± 2.1 mEq/hour in the early postoperative studies. Between the early and later postoperative studies, secretory values rose in two patients and fell in two, but the average changed only slightly (6.3 ± 2.5 mEq/hour). One patient, who showed a good reduction in the early postoperative study, had a return of acid secretion nearly to the preoperative level in the later study.

The 5% amino acid solution proved to be only a fair stimulant of gastrin release. Preoperatively, gastrin values in nine patients who underwent SPV rose from a basal level to 60.9 ± 5.9 pg/ml to a peak of 81.4 ± 10.0 pg/ml at 60 minutes (Fig. 6). At 90 minutes (which was 30 minutes after the pH had been lowered to 2.5) the gastrin value fell to 71.8 ± 6.8 pg/ml. Postoperative stimulated gastrin values in the same patients were significantly higher when tested by analysis of variance; the basal level of 90.6 ± 4.6 pg/ml rose to 108 ± 13 pg/ml at 60 minutes and 112 ± 12.9 pg/ml at 90 minutes.

The preoperative gastrin values of the obstructed patients who underwent truncal vagotomy and drainage were significantly higher than those of the SPV patients

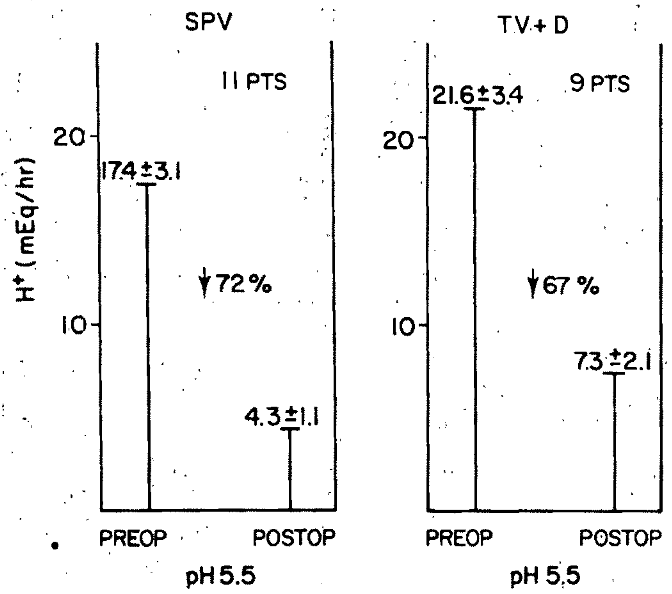

FIG. 4. Mean pre- and postoperative acid secretory values measured by intragastric titration at pH 5.5 in 11 patients treated by selective proximal vagotomy (SPV) and nine patients treated by truncal vagotomy plus drainage (TV + D).

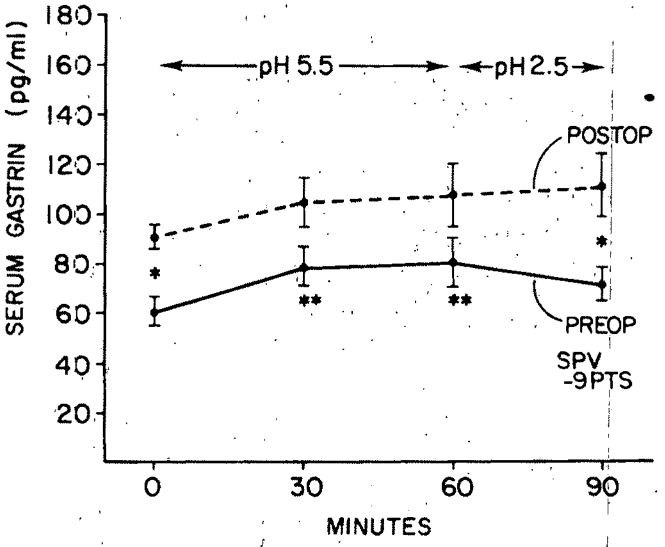

FIG. 6. Serum gastrin responses in nine patients before and after selective proximal vagotomy. Values at 0 time are basal. The amino acid solution was introduced and maintained at pH 5.5 for one hour and then changed to pH 2.5. The single asterisk indicates significant differences between pre- and postoperative patients and the double asterisk indicates significant elevation above basal.

(Table 1). The mean preoperative basal level of six patients was 90.8 ± 18.8 pg/ml, which rose significantly to 163.6 ± 24.7 pg/ml at 30 minutes and 178.6 ± 28.9 pg/ml at 60 minutes. At 90 minutes the value had fallen to 156.6 ± 32.5 pg/ml.

The postoperative gastrin responses of the TV+D patients were significantly higher than those of the postoperative SPV patients, using analysis of variance (Fig. 7). The postoperative 90-minute integrated gastrin value was 2.6 ± 0.7 ng-min/ml for the TV+D patients and 1.3 ± 0.9 ng-min/ml for the SPV patients.

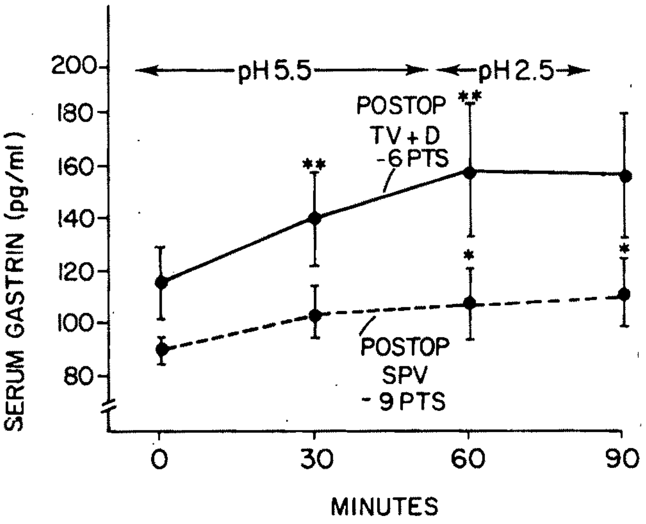

Fig. 7. Serum gastrin responses after operation in nine patients treated by selective proximal vagotomy and six patients treated by truncal vagotomy plus drainage. The single asterisk indicates differences between postoperative gastrin values in the SPV and TV + D patients, and the double asterisk indicates significant elevations above basal.

Discussion

Our current technique of selective proximal vagotomy includes meticulous dissection of the intra-abdominal esophagus as advocated by Hedenstedt[9] and by Hallenbeck and colleagues.[8] In the early studies reported here, this technique affords a degree of acid reduction that appears to be safe and reliable and is certainly comparable to that achieved by the standard truncal vagotomy. The two groups studied are clearly not comparable; those patients operated upon by truncal vagotomy were all obstructed before operation. Nonetheless, the degree of acid reduction in the two groups is equal to or greater than that commonly achieved by other standard procedures.[29,31] It is certainly greater than the degree of acid reduction we have previously reported with SPV (about 50% of MAO)[32] before we adopted the technique of skeletonizing the intra-abdominal esophagus. Reports of reduction of acid output (basal and maximal after pentagastrin (Pg) and Histalog (H)) in seven recent studies are summarized in Table 2. Jordan[15] reviewed the secretory results in 581 patients in seven different series and found reductions of basal acid output that ranged between 20–81% and of maximal acid output that ranged between 25–98%.

Measurement of acid secretion at pH 2.5 and 1.5 in both SPV and TV+D patients confirmed the inhibitory effect of low intragastric pH on acid secretion.[17,30,32] It is of interest that the preoperative TV+D patients with gastric outlet obtruction showed less inhibition of acid secretion by the lower pH levels than did the nonobstructed SPV patients (Fig. 5).

Table 1. *Gastrin Concentration at pH 5.5 (pg/ml)*

	Basal	After introduction of AA meal	
		30 minutes	60 minutes
SPV (n = 9)			
Preop	60.9 ± 5.9	78.7 ± 8.4*	81.4 ± 10.0*
Postop	90.6 ± 4.6†	104.9 ± 10.2	108.2 ± 13.0
TV + D (n = 6)			
Preop	90.8 ± 18.8	163.6 ± 24.7*	178.6 ± 28.9*
Postop	116.5 ± 13.7	141.5 ± 18.5*	159.6 ± 25.9*

* Significantly elevated above basal.
† Significantly elevated over preop values.

The acid data presented here and in Table 2 give clear evidence that the technique of SPV has evolved to the point that safe and predictable levels of reduction of acid output can be achieved. As noted by Amdrup and colleagues,[1] the evolution of a new surgical procedure is a dynamic process with addition of improvements and refinements,[8,9] along the way. It is important that each surgeon who adopts the procedure does so after careful familiarization with technique. He should measure the acid reduction (by any standard method) that he achieves in early cases. This is his only test

Table 2. *Reduction of Acid Output after Selective Proximal Vagotomy*

Author	# Patients	% BAO	% MAO	Time Postop
Amdrup et al[1]	93	—	49 (Pg)	1 Yr.
Geurts et al[7]	60	60 72	64 (Pg) 50 (Pg)	14 days 6 Mos.
Hedenstedt[9]	48	85	75 (H)	1 Mo.
Jepson et al[11]	26 20	— —	48 (Pg) 52 (Pg)	1 Wk. 1 Yr.
Jordan[16]	27	43	47 (H)	2 Yrs.
Roland et al[20]	9	—	50 (Pg)	6 Mos.
Thompson et al[31]	23	80	50 (H)	2 Mos.

Pg = pentagastrin
H = Histalog

of the adequacy of denervation. If properly done, the technique appears safe and reliable and it is time for widespread critical evaluation.

Basal and stimulated levels of serum gastrin were higher preoperatively in the obstructed patients later operated upon by truncal vagotomy than in the preoperative SPV patients (Table 1). This confirms the widespread clinical impression that patients with gastric outlet obstruction often manifest varying degrees of hypergastrinemia, an impression that has been carefully documented by Tani and Shimazu.[27]

Postvagotomy increases in basal and food-stimulated gastrin levels have been demonstrated repeatedly.[24,28,30] This increase formerly was ascribed to simple loss of acid inhibition after vagotomy, but Debas, Walsh and Grossman[3] showed that postvagotomy augmentation of gastrin release could be blocked by atropine, which suggested that the vagus exerts an inhibitory influence on cholinergic mechanisms for gastrin release. Stadil and Rehfeld[24] showed that the mean increase in gastrin after truncal vagotomy was higher than after selective gastric vagotomy; they proposed that extragastric vagal branches suppress release of gastrin. Malmstrøm and colleagues[19] showed that truncal vagotomy caused an increase in the gastroduodenal mucosal content of gastrin, which suggests that the vagus suppresses gastrin production. In studies on the effect of vagotomy on the actions of bombesin and somatostatin on gastrin release in dogs, we found that vagotomy caused an increase in release of gastrin after bombesin and food and an augmentation of somatostatin suppression of food-stimulated gastrin release.[22] We suggested that vagotomy causes a loss of both stimulatory and inhibitory vagal effects on gastrin release.

Sjödin[23] showed that sham feeding inhibited pentagastrin-stimulated acid secretion in Heidenhain pouch dogs. This inhibition was not affected by extragastric abdominal vagotomy (contrary to previous findings[24]), but was reduced or abolished after truncal vagotomy. He suggested that vagal stimulation releases a hormone from the main stomach or duodenal bulb, which has an inhibitory action on gastric acid secretion.

The findings in the present study that the postoperative gastrin levels are higher after selective proximal vagotomy at both pH 5.5 and 2.5 provide strong evidence that the postoperative increase is not due to change in acid secretion since the intragastric pH was maintained at constant levels before and after operation (Fig. 6). Moreover, since the vagal innervation of the antrum is intact in the postoperative patient, the rise in gastrin is not due to loss of vagal inhibition of antral gastrin release. The results are consistent with Sjödin's hypothesis,[23] and further, suggest that the hormonal agent arises from the gastric fundus since it is the only segment of the gut denervated by SPV. The findings that postoperative gastrin levels are higher in patients with truncal vagotomy than with SPV (Fig. 7) might be a consequence of a persistence of high preoperative gastrin levels in the obstructed patients, or (if this is proven to persist in later postoperative studies), it might be caused by a further direct vagal inhibition of antral release of gastrin. The numbers of patients are not large and the changes in gastrin output are not great. They do provide a suggestion.

The 5% amino acid solution used in the present study evoked an acid output of pH 5.5 that was 49% of the maximal acid output to Histalog in the nonobstructed SPV patients; the same patients had a gastrin response (peak minus basal) at pH 5.5 of 21 pg/ml. The 10% amino acid solution previously used[30] gave an acid output in nonobstructed patients with duodenal ulcer that was 73% of the maximal acid output to Histalog at pH 5.5, and a gastrin response of 90 pg/ml. We changed to the present iso-osmolar 5% solution because of concern that the moderately hypertonic 10% solution (575 mosm) might inhibit acid and gastrin release.[26] In sum, the 10% solution appears to be the better stimulant and we will use it in the future.

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DISCUSSION

DR. JOHN LAZELLE SAWYERS (Nashville, Tennessee): I'm delighted to hear Dr. Thompson's and his colleagues' results from their gastrointestinal laboratory that selective proximal vagotomy is as effective as truncal vagotomy and drainage in reducing acid secretion.

Last year Dr. Herrington and I reported to this society our results from a prospective randomized study comparing selective proximal vagotomy with selective gastric vagotomy and pyloroplasty. Basal acid output was reduced after operation by 75% in patients having selective proximal vagotomy and 86% in patients having selective gastric vagotomy and pyloroplasty. This difference was not significant.

Acid secretion studies on these patients were done at three months, one year and two years postoperatively. There was no significant difference between the results at these various time intervals. However, when we performed Hollander tests following the basal acid output, we found that there was a 30% increase in positive Hollander tests by the end of two years. These findings are consistent with those reported from Leeds by David Johnston and Professor Goligher in that basal acid outputs have remained low, but there has been an increase in the incidence of positive Hollander tests; and I wonder if Dr. Thompson would comment on that in his closing.

We continue to be enthusiastic about selective proximal vagotomy in patients requiring operation for duodenal ulcer. In more than 300 patients, with follow-ups extending now to six years, we have good to excellent results in over 90% of patients. The ulcer recurrence rate is 2%, and the incidence of postgastrectomy sequelae, of dumping, reflux gastritis and postvagotomy diarrhea remains very low.

Dr. Thompson's presentation adds further support for adopting selective proximal vagotomy, or proximal gastric vagotomy, as we prefer to call it, as the operation of choice in patients with nonobstructive chronic duodenal ulcer.

DR. LLOYD M. NYHUS (Chicago, Illinois): There seems to be a slowly increasing recurrent ulcer rate following SPV being reported by investigators throughout the world. This recurrence rate is now averaging around 10%. It also seems that after a year or two, basal and stimulated acid secretion is also increasing after SPV.

In your report, Dr. Thompson, you indicate that your studies of acid were made at four and six weeks. It will be interesting to see what happens to the gastric acidity as time goes by.

On Dr. Thompson's slide relative to truncal vagotomy it was apparent that the decrease in acid output was less than after SPV. What kind of vagotomy technique does Dr. Thompson use? I would assume it's the so called Dragstedt technique of carefully finding the main trunks and carefully assuring ourselves that there are no residual periesophageal vagal fibers.

It is my opinion that we must take a second look at the technique for performance of truncal vagotomy. When we do a truncal vagotomy, we should be as extensive in our proximal dissection as proposed by Goligher and Hallenbeck.

In other words, with SPV, selective proximal vagotomy, a major point is made about clearing 5 cm of the lower end of esophagus, as well as from the left and from the right, to be certain that the "criminal nerves of Grassi" are not missed. We must look for these extravagal fibers when performing truncal vagotomy. The reason we have a 30% incomplete vagotomy in the United States after truncal vagotomy relates directly to this technical fact. We do not do an extensive enough dissection of vagal fibers in the area of the distal esophagus while performing truncal vagotomy. I would like Dr. Thompson to comment on this.

DR. LAWRENCE W. WAY (San Francisco, California): This is a very interesting study. The previous discussants have concentrated on the clinical aspects of proximal gastric vagotomy. I wish to emphasize the suggestion from Dr. Thompson's data, that the vagus may possess the capacity to inhibit gastrin release. This is an interesting physiological question that a number of people have addressed in a variety of ways.

We performed some experiments several years ago that were somewhat similar to these, in that we controlled intragastric pH but stimulated the stomach with insulin hypoglycemia with a technique of partial vagotomy by cooling the nerves in the neck. We found that the gastrin levels increased, suggesting the same thing as Dr. Thompson, that the vagus inhibits gastrin release, but he's taken it several steps further by doing the experiment in humans and developing an analysis that implicates the fundus.

I would like to ask Dr. Thompson whether the truncal vagotomy patients are proper controls for the proximal gastric vagotomy patients because other studies in recent years have shown that the effect of truncal vagotomy on the pancreas, for example, is substantial. There is a good deal less enzyme output into the duodenum. Also, one could expect gastric emptying to be somewhat more rapid in his truncal vagotomy patients, and I am not quite certain how these might have affected his results, but there are some significant differences between these two groups, and I would appreciate his consideration of this question.

DR. JAMES C. THOMPSON (Closing discussion): I am grateful to Drs. Sawyers, Nyhus, and Way.

Dr. Sawyers talked about the high level of positive postoperative Hollander tests, and as far as I am concerned, that is one more nail, *e pluribus unum*, for dropping the Hollander test. I think, when you analyze carefully the data that Dr. Johnston has reported, in which he has a 90% positive Hollander test at four years, and yet he has had only two or three recurrences in several hundred, it is easy to see that the Hollander test is not a good predictor of recurrent ulcer.

Furthermore, as I and many others have said before, there are many other things that are wrong with the Hollander test. It is dangerous to perform. There have been ten people who have reportedly died from it and that's the kind of news I wouldn't rush into print with, so there are probably a lot more.

The information that you want to get from a Hollander test can be secured from other secretory tests that are not so dangerous. Furthermore, the anatomic basis of the Hollander test, I think, has been fairly thoroughly disproven. It does not depend upon the anatomic integrity of the vagus. If you do a simple 50% distal gastrectomy without vagotomy in man, you get about a 30% incidence of negative Hollander tests. It simply reflects the secretory capacity of the stomach. I do not think it is worthwhile, and I think there are a lot of other tests that are just as good.

Dr. Nyhus commented upon the high recurrence rate that now has been reported following SPV, and I am told by the grapevine that Professor Goligher has said in his last lecture tour of the country that he may go back to truncal vagotomy. What we are now seeing is the recurrence of those early cases which did not, in fact, have the extensive esophageal resection that has been advocated by Dr. Hedenstedt and by Dr. Hallenbeck of this Association.

As Amdrup has said in his beautiful article in the *World Journal of Surgery*, in which he analyzed the recent history of SPV, the evolution of this operation is such that we should just now be beginning our controlled clinical trials. We have just now arrived at a safe and reproducible way of operating on these patients.

I think, Lloyd, that the difference between 67% reduction in the truncal vagotomy patient and the 72% in the SPV patients is really not significant at all. Perhaps if you do a more extensive and time consuming and meticulous dissection with truncal vagotomy, you will get better results. I would certainly advocate that.

Dr. Way asked whether truncal vagotomy patients really serve as a control for these selective vagotomy patients; in fact, of course, they do not. It is a totally different operation. They were selected, in fact, to serve as a contrast, to see whether or not we could achieve similar degrees of acid reduction. The data that we have on serum gastrin came as a present, as a prize.

The persistence of the high serum gastrin level postoperatively in the truncal vagotomy patients may mean that the very high, obstructed, preoperative level simply persisted for two or three months after operation, or it may be a real phenomenon, and only time will tell. I certainly agree with Dr. Nyhus that what we really need to do is to follow these patients for two or three or five years before we know.

Relief of Acute, Persistent Postvagotomy Atony by Metoclopramide

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Seventeen patients with acute, persistent postvagotomy atony after vagotomy with antrectomy or pyrloroplasty for peptic ulcer underwent a doubleblind study of the relief of postvagotomy atony by metoclopramide. All patients had complete, functional gastric obstruction for at least three weeks postoperatively, precluding oral alimentation. Contrast studies and gastroscopy ruled out mechanical obstruction in each patient. Gastric outlet obstruction was confirmed by radioisotope assessment of gastric emptying of a special solid meal labeled with Technetium 99m DTPA. A gamma camera over the epigastrium precisely quantitated the emptying rate of the labeled meals. After baseline scanning an intravenous placebo was given to each patient and all 17 showed gastric retention of the meal after 90 minutes. Gastric emptying rates were restudied 24 hours later after intravenous metoclopramide and all 17 patients then immediately emptied the labeled meals. These patients then received standard postgastrectomy diets. Eight patients received metoclopramide tablets (10 mg 30 minutes a.c., q.i.d.) and nine received placebo tablets. Each of the eight patients receiving metoclopramide ate normally immediately after treatment with no further evidence of gastric atony. The nine patients receiving the placebo were unable to retain any oral feedings and were then given oral metoclopramide which promptly relieved gastric atony. All 17 patients received metoclopramide for one month without side effects after which the drug was discontinued with no recurrence of gastric symptoms during follow-up periods ranging from three to 27 months. Metoclopramide safely and effectively relieves acute, non-mechanical gastric atony when this occurs after surgical treatment of peptic ulcer.

ACUTE, SEVERE functional gastric outlet obstruction is defined as the inability of the stomach to empty liquids or solids through a mechanically patent gastroenteric stoma into the upper small intestine for more than three weeks after surgical treatment of peptic ulcer disease. This condition is also referred to as gastric atony. Various reports indicate that the overall incidence of severe atony ranges from 0.5% to 3% of all patients who undergo various surgical procedures for peptic ulcer disease; however, the incidence of severe atony may rise to approximately 8% among patients who have truncal vagotomies and gastric drainage procedures (pyloroplasty or gastroenterostomy) in the presence of chronic pyloric obstruction that has caused pronounced dilatation and edema of the stomach.[1,2,5,7,10,13] Approximately 25–50% of those who develop severe functional gastric outlet obstruction immediately after surgical treatment for peptic ulcer disease require re-exploration to rule out mechanical obstruction. The mortality rate following re-operation of these patients ranges from 0% to 12%.[1]

From January 1, 1976 through January 31, 1978 a study was done at The University of Texas Southwestern Medical School in Dallas to determine the effectiveness of metoclopramide in treating complete, non-mechanical gastric outlet obstruction in patients undergoing surgical treatment of peptic ulcer disease. Metoclopramide is a pharmacologic agent that enhances peristalsis in the esophagus, stomach, duodenum, and small bowel.[16]

Materials and Methods

Non-mechanical, complete gastric outlet obstruction occurred immediately after surgery and persisted for more than three weeks in 18 patients operated upon for duodenal ulcer and in two operated upon for gastric ulcer at the Parkland Memorial Hospital and the Veterans Administration Hospital in Dallas during the 25 months of this study. There were 18 males and two females in this series of patients; the ages of these patients ranged from 29 to 70 years (average age was 51 years). The chief indications for surgical treatment were hemorrhage in 11 of the 20 patients and intractable pain in nine; none had gastric outlet obstruction preoperatively. Five patients had vagotomy and pyloro-

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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plasty, four had vagotomy-antrectomy (Billroth I), and 11 had vagotomy-antrectomy (Billroth II).

In each of these 20 patients, as soon as intractable vomiting became apparent, barium upper gastrointestinal contrast studies were done. None of the contrast studies demonstrated mechanical obstruction, whereupon all 20 patients were treated by discontinuance of oral intake, re-institution of constant nasogastric suction, and central intravenous hyperalimentation. This regimen was continued until the twenty-first postoperative day in each patient, to permit possible spontaneous resolution of gastric outlet obstruction; however, spontaneous recovery occurred in none of the 20 patients in this study. On the twenty-first postoperative day barium upper gastrointestinal series were repeated. Fiberoptic gastroscopy was performed at this time and this study demonstrated a widely patent gastroenteric stoma in each of the 20 patients. After the endoscopy showed a patent stoma, the percentage of ingested food retained within the stomach was exactly quantitated by measuring the rate at which a standard radioactive labeled solid meal emptied from the stomach. This measurement was done with a gamma camera interfaced with a computer, using a recently described isotopic method for exactly measuring the rate of gastric emptying.[6,17] The standard meal consisted of a scrambled egg and a piece of dry toast, covered with a portion of butter containing 1 mCi of Technetium-99m DTPA. Over a period of about two minutes the labeled meal was chewed thoroughly and swallowed with six ounces of water to insure even distribution of the meal within the stomach. Immediately after the labeled meal was eaten, the patient was immobilized in a semi-reclining position in a special chair and the gamma camera was fixed directly over the epigastrium. The camera was centered over the area of maximal radioactivity within the stomach by oscilloscopic visualization. Five minutes after consumption of the meal, the number of gamma counts in the stomach was recorded by the gamma camera and computer and immediately after determination of the baseline counts, a placebo solution was given intravenously to each patient. Gamma counts from the stomach were recorded within the computer via the gamma camera interface every five minutes for 90 minutes after injection of the placebo solution. Also, at intervals of 30 minutes, the progress of the labeled meal out of the stomach was recorded photographically by the gamma camera. Figure 1 shows a photographic record of normal gastric emptying, Fig. 2 shows abnormally delayed gastric emptying consistent with gastric atony, and Fig. 3 shows abnormally delayed gastric emptying, but with significant improvement of emptying by intravenous metoclopramide. The gastric emptying rate was calculated exactly from the rate of disappearance of gamma counts from the stomach. If, after 90 minutes of counting, more than 50% of the meal remained in the stomach, the diagnosis of gastric outlet obstruction was confirmed. Normal individuals retain less than 50% of the labeled meal after 90 minutes as confirmed by studies of gastric emptying in 15 normal control subjects. Figure 4 graphically depicts the gastric emptying rates of each of the 15 normal control subjects (percentage retention of the labeled meal in normal subjects ranged from 10% to 50% at 90 minutes; average retention was 29%.)

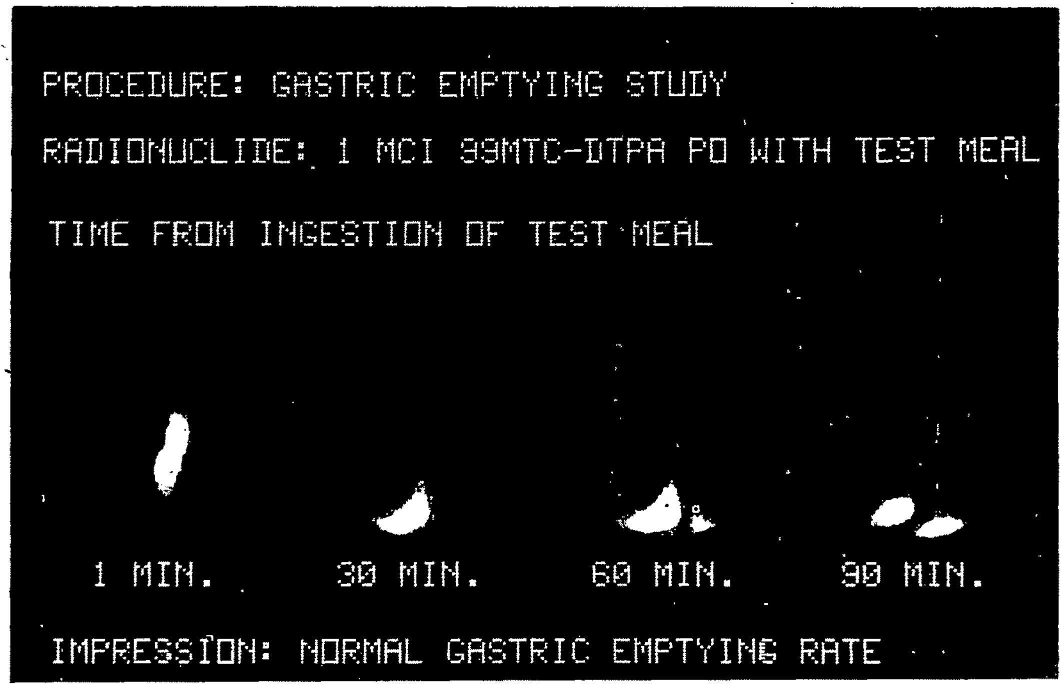
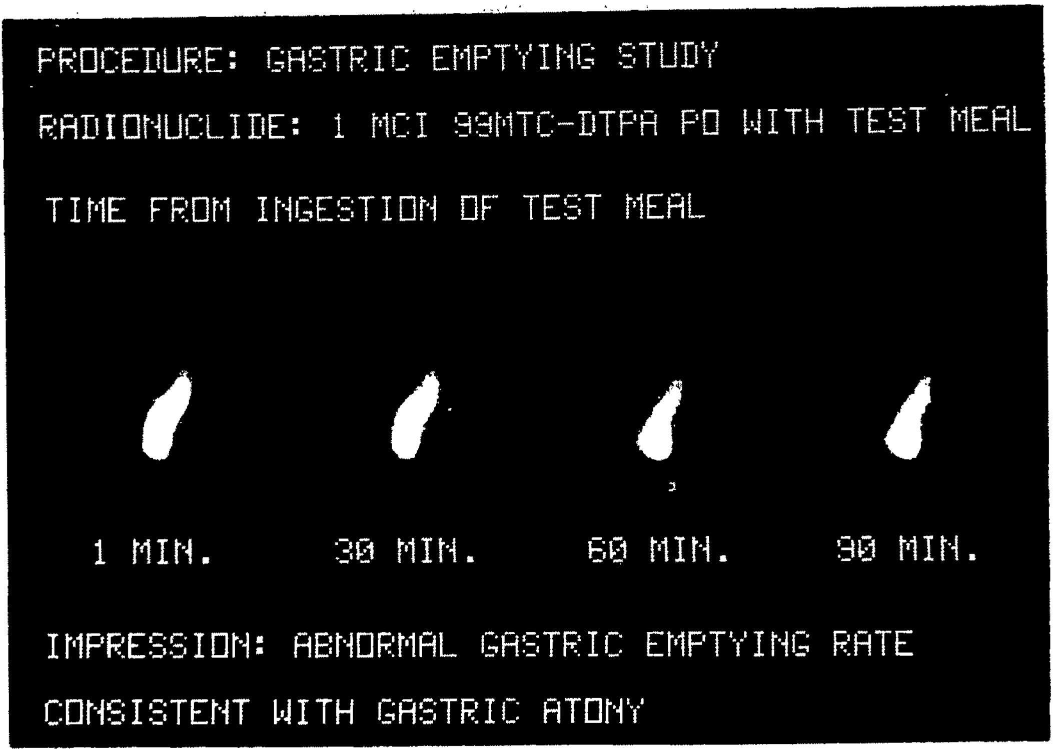

PROCEDURE: GASTRIC EMPTYING STUDY
RADIONUCLIDE: 1 MCI 99MTC-DTPA PO WITH TEST MEAL
TIME FROM INGESTION OF TEST MEAL
1 MIN.
30 MIN.
60 MIN.
90 MIN.
IMPRESSION: NORMAL GASTRIC EMPTYING RATE

FIG. 1. Gamma camera photographs showing sequential emptying of a normal stomach during a 90-minute period after ingestion of a radio-isotope labeled solid meal.


PROCEDURE: GASTRIC EMPTYING STUDY

RADIONUCLIDE: 1 MCI 99MTC-DTPA PO WITH TEST MEAL

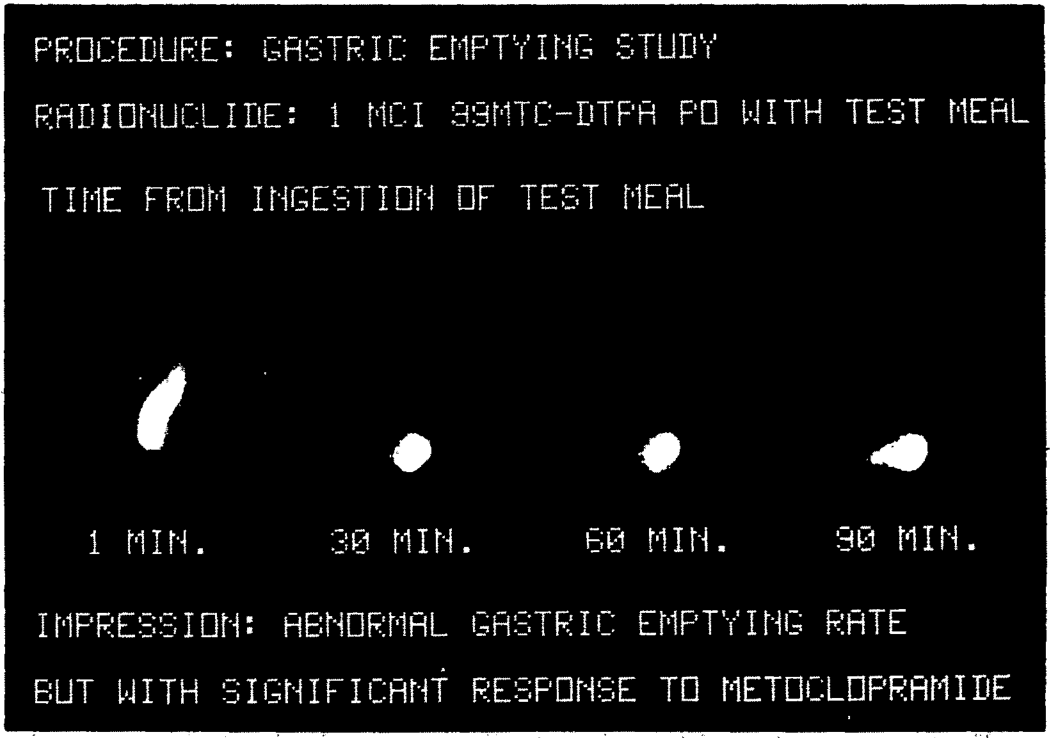
TIME FROM INGESTION OF TEST MEAL

IMPRESSION: ABNORMAL GASTRIC EMPTYING RATE
CONSISTENT WITH GASTRIC ATONY

FIG. 2. Gamma camera photographs showing failure of emptying of an atonic stomach (postvagotomy-antrectomy, Billroth II) during a 90-minute period after ingestion of a radioisotope labeled solid meal.

Results

In all 20 patients in this study initial radioisotope measurement of gastric emptying documented gastric outlet obstruction that was not alleviated by an intravenously-injected placebo solution. Figure 5 graphically depicts the failure of the intravenously injected placebo solution to relieve gastric outlet obstruction. In these 20 patients the amount of the labeled meal retained in the stomach after 90 minutes ranged from 70% to 100% and the average amount retained was 94%. However, when radioisotope gastric emptying studies were


PROCEDURE: GASTRIC EMPTYING STUDY

RADIONUCLIDE: 1 MCI 99MTC-DTPA PO WITH TEST MEAL

TIME FROM INGESTION OF TEST MEAL

IMPRESSION: ABNORMAL GASTRIC EMPTYING RATE
BUT WITH SIGNIFICANT RESPONSE TO METOCLOPRAMIDE

FIG. 3. Gamma camera photographs showing significant improvement of emptying of an atonic stomach (postvagotomy-antrectomy, Billroth II) during a 90-minute period after ingestion of a radioisotope labeled solid meal and an intravenous injection of metoclopramide.

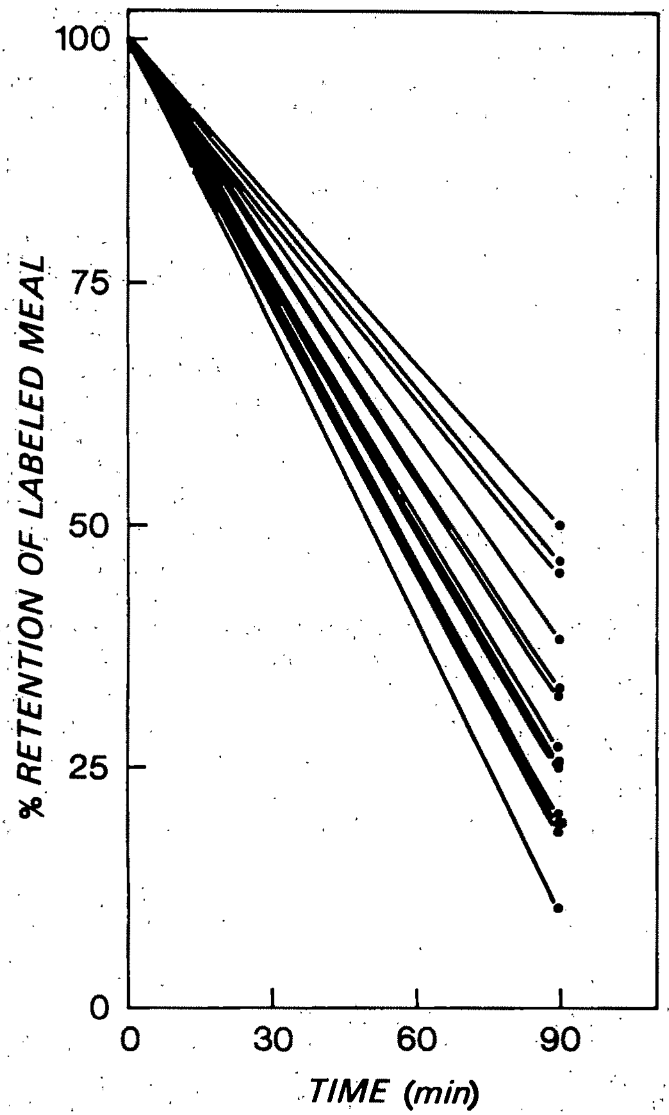


FIG. 4. Percentages of gastric emptying 90 minutes after ingestion of a radio-isotope labeled solid meal in 15 normal individuals with intact stomachs.

repeated 24 hours later, immediately after an intravenous injection of metoclopramide (0.3 mg/kg body weight), it was noted that gastric emptying became normal or markedly improved in 17 of the 20 patients as shown in Fig. 6. In these 17 patients immediately after intravenous metoclopramide the percentage retention of the labeled meal ranged from 13% to 72% at 90 minutes; average retention was 48%. Three patients did not respond. These three patients were re-explored and each was found to have high grade efferent loop obstruction due to adhesions, lysis of which relieved gastric outlet obstruction.

Twenty-four hours after radioisotope studies documented marked improvement of gastric emptying by intravenous metoclopramide, each of the 17 patients was placed on a standard postgastrectomy diet consisting of six small solid feedings daily. In addition, each of the 17 patients received either a 10 mg metoclopramide tablet or placebo tablet of identical appearance 30 minutes before meals, four times daily. Patients were chosen to receive metoclopramide or placebo tablets on a randomized, double-blind basis. Subsequent analysis of the medication code after the study was completed showed that eight patients initially received metoclopramide tablets (Group I patients), and nine initially received placebo tablets (Group II patients). All Group I patients ate without vomiting or other symptoms immediately after oral metoclopramide therapy began and had no further evidence of impaired gastric emptying.

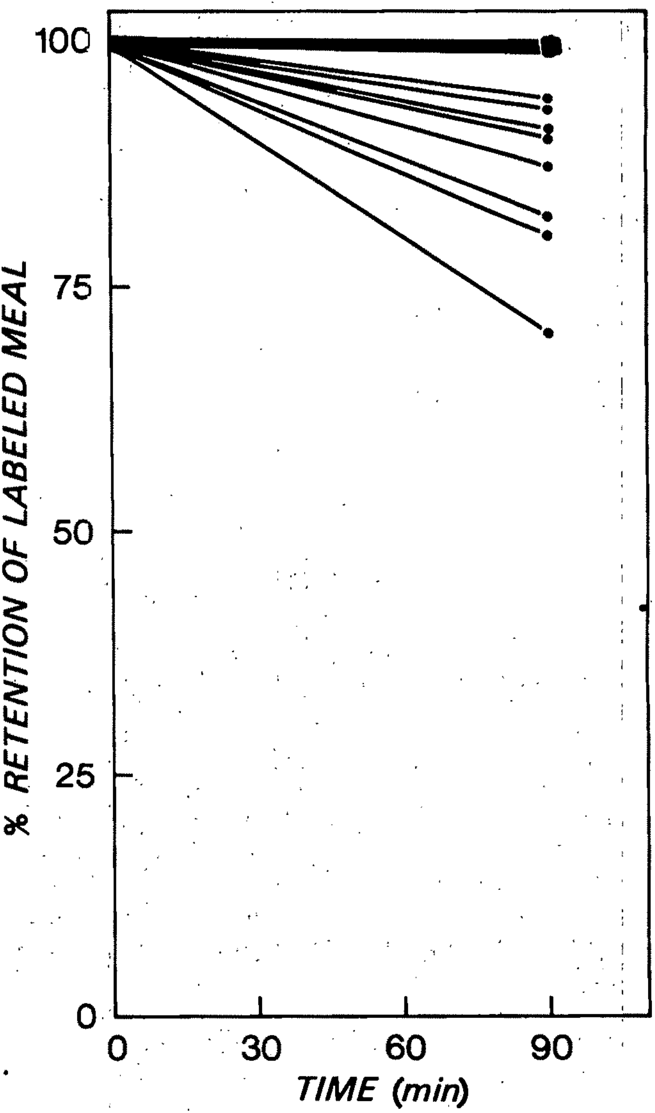


FIG. 5. Percentages of gastric retention 90 minutes after ingestion of a radio-isotope labeled solid meal in 20 patients with gastric outlet obstruction (functional or mechanical) following gastric surgery for peptic ulcer disease.

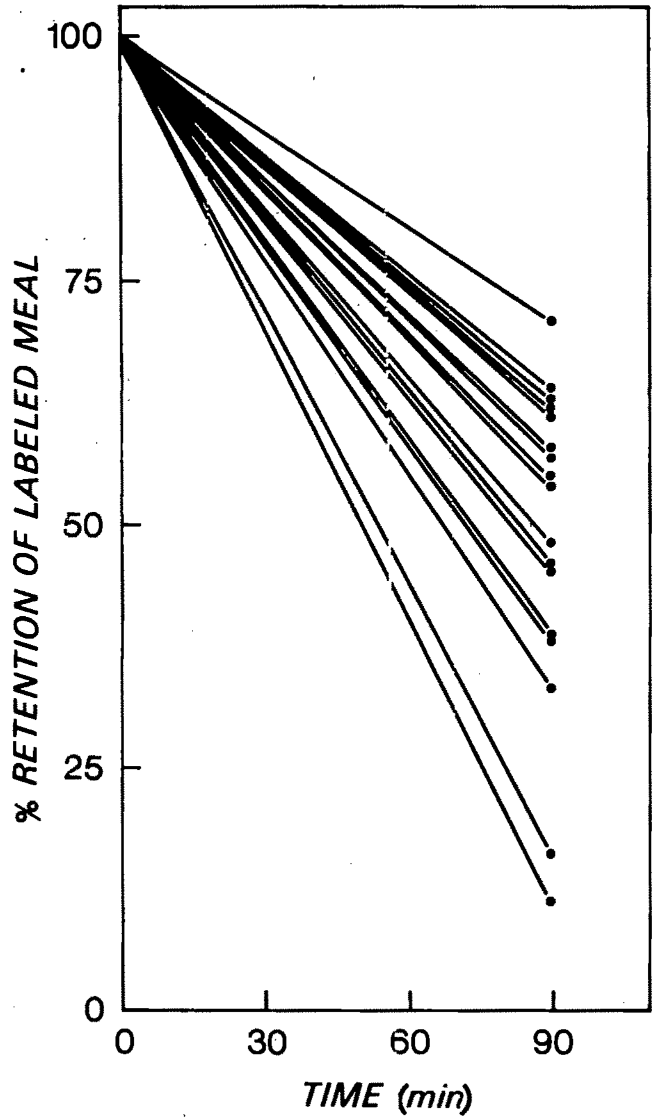


FIG. 6. Improvement of gastric emptying by intravenous metoclopramide in 17 patients with *functional* gastric outlet obstruction after surgical treatment of peptic ulcer disease (90 minutes after ingestion of radio-isotope labeled solid meal).

In contrast, it was immediately apparent that the nine Group II patients were receiving placebo instead of metoclopramide tablets because these patients developed intractable nausea and vomiting of all ingested material within less than 24 hours after institution of oral feeding. Because of the severe nausea and vomiting in the patients receiving placebo tablets, it was necessary to place them on oral metoclopramide which immediately and permanently relieved their symptoms of gastric outlet obstruction. Group I and Group II patients then remained on oral metoclopramide, 10 mg four times daily before meals, for 28 days. None of these 17 patients has had any further evidence of gastric outlet obstruction or other significant gastrointestinal symptoms during close follow-up ranging from three to 27 months.

Metoclopramide caused no side effects when given intravenously or orally to any of the patients in this study.

Discussion and Conclusion

Some investigators contend that the stomach pouch, after gastric resection, empties by gravity and not by gastric peristalsis.[10] If this concept is valid, peristaltic stimulants should not improve gastric emptying when stomach evacuation is impaired after gastrectomy, and it would follow that all instances of gastric outlet obstruction after surgical treatment of peptic ulcer disease would be entirely due to mechanical causes instead of gastric atony. However, several observations indicate that impaired motor activity in the proximal stomach after gastric resection may cause severe and persistent gastric outlet obstruction. First, mechanical obstruction is not detected in many patients who are reexplored, because of persistent gastric retention after gastrectomy.[1,2,5,7,12,13] Second, several recent studies show that metoclopramide enhances proximal gastric peristalsis and relieves chronic symptoms of gastric retention due to delayed emptying of the stomach which occasionally develops several months or years after gastric surgery.[3,4,15,18,19] Third, the present study indicates that metoclopramide markedly improves proximal gastric peristalsis and consistently relieves acute symptoms of severe gastric retention that may develop immediately after surgical treatment of peptic ulcer disease in a few patients.

Metoclopramide is the generic name of N(diethylamino-ethyl)-2-methoxy-4-amino-5-chlorobenzamide. This agent is closely related chemically to procainamide, but pharmacologically has no procainamide activity.[16] Metoclopramide was first synthesized in 1961 and was introduced as a therapeutic agent in 1964 by Justin-Besancon and associates.[11] Since then the drug has been used extensively in Europe and South America as an antiemetic and for the treatment of esophageal reflux and postoperative ileus. Metoclopramide also facilitates duodenal or small bowel intubation and upper gastrointestinal barium contrast studies. The use of metoclopramide for these purposes depends upon the following actions of this agent: 1) suppression of the emesis center in the medulla oblongata, 2) stimulation of esophageal peristalsis, 3) enhancement of lower esophageal sphincter tone, 4) relaxation of the pyloric sphincter; and 5) stimulation of duodenal and small bowel peristalsis.[8,9] Jacoby and Brodie, and James and Hume first reported that metoclopramide stimulates gastric peristalsis and emptying.[8,9] Stadaas and Aune, in 1971, first noted that metoclopramide relieved gastric stasis in man following surgical treatment of peptic ulcer disease.[18] In 1972, Stadaas and Aune reported a study of 12 patients who had severe manifestations of chronic gastric retention after surgical treatment for peptic ulcer disease.[19] The operations on these 12 patients were performed two or three years before oral metoclopramide therapy was given. Marked relief of chronic gastric stasis was achieved by eight of these 12 patients, but symptoms promptly returned when metoclopramide was discontinued.

In 1974, Hancock and associates also reported that acute, as well as chronic, gastric retention responded to metoclopramide.[4] These investigators studied gastric emptying by gamma camera scanning of the stomach after ingestion of an isotopically labeled solid meal in ten normal patients and in ten patients who had undergone vagotomy and pyloroplasty an average of 15 days before gastric emptying was studied. Hancock and his colleagues found that intravenous metoclopramide had no effect on gastric emptying in the ten normal subjects nor in four postvagotomy patients who had normal postoperative gastric emptying times (50% emptying within 30–150 minutes). However, in six postvagotomy patients who had abnormal gastric retention of the labeled meal (50% emptying after an average of 369 minutes), intravenous metoclopramide significantly improved gastric emptying (50% emptying within an average of 194 minutes).

In 1976, Metzger and associates also reported that metoclopramide effectively relieved symptomatic chronic gastric retention in six patients who underwent vagotomy and gastric resection at least four months before receiving metoclopramide.[15] Radiographic and gastroscopic studies ruled out mechanical obstruction as a cause of gastric retention in these six patients. Metzger and his colleagues also measured gastric emptying by means of the gamma camera technique. They found that in comparison to an intramuscular injection of a placebo, an intramuscular injection of metoclopramide produced a 2.6 fold increase in gastric emptying during a 90 minute scanning period.

The most recent study of metoclopramide therapy of chronic gastric retention after gastric surgery was reported by Davidson and associates.[3] These investigators studied 20 patients who developed severe manifestations of chronic gastric retention after various surgical procedures for peptic ulcer disease. The 20 patients in this study received oral metoclopramide, 10 mg three times daily before meals for two to four weeks. Excellent or good relief of chronic gastric retention was achieved by 45% of these 20 patients, fair relief by 25%, and no relief by 30%. In all 20 patients, symptoms of chronic gastric retention promptly reappeared when metoclopramide was discontinued.

The mechanisms by which metoclopramide improves gastric motor activity are poorly understood; however, there is some evidence that metoclopramide indirectly suppresses intrinsic neural plexuses within the gastric wall that inhibit gastric motility. In the intact stomach these intrinsic inhibitor neurons are normally overridden at regular intervals by extrinsic vagal impulses and by intrinsic neural plexuses that stimulate gastric peristalsis and cause gastric emptying. After gastric surgery, and especially after vagotomy in the presence of a dilated and edematous stomach due to chronic pyloric obstruction, the inhibitor neural plexuses within the gastric wall may be virtually unopposed by the neural mechanisms that normally stimulate gastric motility. The inhibitor neurons in the gastric wall depend upon dopamine for their inhibitory effect. Valenzuela has shown that metoclopramide may block the effect of dopamine on the inhibitor neurons in the gastric wall; therefore, metoclopramide may induce normal gastric motility by blocking the effect of dopamine on the inhibitor neurons. This, in turn, would permit unopposed activity of the neural plexuses within the stomach wall that normally stimulate gastric peristalsis and emptying.[20]

Metoclopramide is available only as an investigational drug in the United States. It has, however, been used without significant side effects for more than a decade outside this country. In a very few patients, temporary extrapyramidal side effects may be caused by metoclopramide. Occasionally, mild and transient agitation and motor restlessness may follow administration of intravenous metoclopramide, but true dystonic reactions occur in only about 1% of patients receiving this agent. These dyskinesias are noted most commonly in young patients and consist of trismus, torticollis, facial spasms, opisthotomos, and oculogyric crises. When they occur, extrapyramidal reactions develop within 36 hours after metoclopramide is given and usually disappear within 24 hours after the drug is discontinued; these reactions respond rapidly to treatment with anti-Parkinsonian drugs, such as intramuscular diazepam or benztropin.[16]

The principal reason the Food and Drug Administration has not released metoclopramide for general usage in the United States is that this agent is a potent stimulator of prolactin release in both sexes. Prolactin levels have been observed by McNeilly and associates to increase three to eight fold within five minutes after an intramuscular or intravenous injection of 10 mg of metoclopramide and about 60 minutes after oral administration of this quantity of the drug.[14] Obviously, it is possible that chronic usage of metoclopramide might incite carcinoma of the breast although, at present, there is no evidence to support this speculation. Parenteral metoclopramide will soon be released for single dose usage in the United States. When used in this manner, the agent is helpful in the performance of radiographic studies of the upper gastrointestinal tract, gastroduodenal endoscopy, and intubation of the duodenum and small bowel.[8,9] The excellent response of acute functional gastric outlet obstruction to oral metoclopramide noted in the 17 patients reported in this paper suggests that this agent should be released for short term use (i.e. four to six weeks) for treatment of the occasional patient who develops severe gastric atony that persists for more than three weeks after gastric surgical procedures.

Summary

Seventeen patients who had persistent functional gastric outlet obstruction for more than three weeks after various operations for peptic ulcer disease were studied. Upper gastrointestinal contrast studies with barium and fiberoptic gastroscopy were performed on all patients and, in each case, these studies ruled out mechanical obstruction. Also, the rates of gastric emptying were studied in each patient by the determination of the rate of disappearance of a radioisotope labeled meal from the stomach. Assessment of evacuation of the labeled meal from the stomach was done with a gamma camera placed over the epigastrium. These studies showed severe functional gastric outlet obstruction in all 17 patients in this study. Intravenous metoclopramide caused prompt gastric emptying in each of these 17 patients. All patients then received oral metoclopramide for four weeks with complete and permanent resolution of all symptoms of gastric outlet obstruction. No side effects were caused by this drug. Follow-up of these patients has shown no recurrence of gastric outlet obstruction for periods ranging from three to 27 months after cessation of metoclopramide therapy. It is concluded that oral metoclopramide is an effective and safe treatment for acute, non-mechanical gastric outlet obstruction that occasionally occurs after surgical treatment for peptic ulcer disease.

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DISCUSSION

DR. M. MICHAEL EISENBERG (Minneapolis, Minnesota): I suppose we see twelve or so patients a year with postgastric surgery atony; approximately half come from our institution and about half are referred in from the outside. I'd like to emphasize and re-emphasize some of the things that Dr. McClelland just pointed out, and I would like to supplement some of them.

Most important, I think, is the necessity to emphasize that before a program such as this is embarked upon, the absence of mechanical outlet obstruction must be ascertained. We haven't found radiology to be of much help in this regard. All the radiologist can tell you is that the barium which is placed in the stomach sits there and doesn't go out. He cannot tell you whether it's a mechanical obstruction or whether it's an intrinsic motor defect in the stomach. So although we do get it, in hopes of picking up a stomach that's emptying but which has small bowel obstructed further down the line, we rely much more heavily on endoscopy, and all of our patients are endoscoped. The endoscopist, in addition to assuring you that you are not dealing with a mechanical obstruction, can also tell you something about the peristaltic action of the stomach, which is often very helpful.

Second of all, and concomitantly with determining whether you're dealing with a mechanical obstruction or an intrinsic motor defect, I think it's very important to make sure that these patients are in a good nutritional state, and particularly that their electrolytes are well balanced, because aberrations in either of these parameters can, in and of themselves, cause gastric atony. Often these patients have been starved for a considerable period of time.

Also, I think it's important to emphasize to residents, to referring physicians, to internists, gastroenterologists, and to ourselves, that the urge to reoperate on these people, once it's established that they are not mechanically obstructed, should be fought off. It's often very difficult not to want to go back in. Not only is it not necessary to operate on these people, if they are not mechanically obstructed, but it serves very little purpose for them to have two stomas, both of which are widely patent and neither of which will empty. So patience and fortitude is important here.

Many of these patients are operated upon two and three times. I happen to have one in the house at the moment.

Finally, I think the title of the article—the term "postvagotomy gastric atony," if I may gently suggest, is a little too specific for this syndrome. If you review the gastric surgery literature of the 1920's and '30's and '40's, and even up into the '60's before vagotomy became popular you will find that this syndrome existed even then, and was widely commented upon. It was variously attributed to long afferent loops, incorrect angulation of the stoma, edema of the stoma, poor choice of suture material, suture line abscesses and other mysterious things. One imaginative and creative writer to whom I apoligize—I do not remember his name—called this syndrome "the reluctant stoma," or "the reluctant stomach"; and I much prefer to use that as a general term. As a matter of fact, I'm sure there are many people in the room who have experienced a poorly emptying gastroenterostomy created prophylactically for an antral carcinoma which was unresectable, but which was not obstructing, or for carcinoma of the head of the pancreas, for which a gastroenterostomy was prophylactically created, only to find that postoperatively the stomach will not empty, although both the duodenum and the new stoma are fully patent.

Lastly, although I have no personal experience with metoclopramide, two of my colleagues, both very experienced gastric surgeons, Dr. Bill Silen and Dr. Paul Jordan, who asked that they be quoted, have had some experience with it, and apparently do not share the enthusiasm for this drug. They have not had as strongly positive results with it.

My experience is with a parasympathomimetic drug. I use Urecholine in these patients. I won't go through the detailed recipe by which we treat them at this point, because it wouldn't be fair to the audience, but it requires a great deal of patience, backtracking, moving forward again, backtracking, and so on, and usually tincture of time is amongst the most important ingredients.

Dr. Lawrence W. Way (San Francisco, California): As an initial comment, I'd like to support the authors' good experience, in contrast with Dr. Eisenberg's remarks, because we have had some patients who have been entered into the controlled trial performed at UCLA, a few of whom benefited and a few of whom did not, but these were patients who had chronic problems with gastric emptying.

The reason I wanted to comment was to mention an experiment we did that studied the effect of hyperalimentation on gastric emptying. We discovered, when testing gastric emptying of solids with a technique similar to that described by Dr. McClelland, that a patient with no functional or mechanical problems with intestinal or gastric motility has substantial inhibition of gastric emptying while on hyperalimentation.

This is clinically relevant because as everyone realizes that in the postoperative situation the patient may be unable to consume a diet. Often as Dr. McClelland mentioned, patients are put on hyperalimentation for several weeks, then tried again on the diet. We have learned that it's important to simultaneously withdraw the hyperalimentation at the same time feeding is reinstituted, to avoid this inhibitory effect of the hyperalimentation which may perpetuate the problem. One could erroneously attribute the failure of the patient to eat to the stomach itself, whereas it may be at least partly due to the therapy the patient is receiving.

I would like to ask Dr. McClelland if his patients were on or off hyperalimentation at the time they were studied.

Dr. George Robert Mason (Baltimore, Maryland): We have had the opportunity at the University of Maryland to use the drug, metoclopramide, for approximately six months. We have extended the use of it slightly, to disorders of esophageal motility as well.

(Slide) We have a series of eleven patients, three with esophageal problems, primarily, and eight of them with gastric problems.

An illustrative history is on the next slide; (slide) the man illustrates, I think, the prompt response you usually see to the administration of metoclopramide. The drug's action is of rather short duration. Its maximum effect is almost immediate when given intravenously, and within minutes when it is given orally. It lasts for approximately 45 minutes to an hour, and is very effective when given with a meal, or immediately thereafter, to clean the stomach out.

In the group of patients that we have followed with malignancy and irradiation, or with chronic degenerative neurologic disease, we have not seen any beneficial responses. However, to support Dr. McClelland, in the remainder of the patients who have had a postvagotomy reluctant stomach—all of these patients have emptied rather well.

I would like to point out one thing about the problems with esophageal motility, which are illustrated somewhat on the next several slides. (Slide) This is an illustration of this patient whose capsule history I have given you, showing a dilated esophagus prior to the administration of metoclopramide.

(Slide) This slide shows a quickly emptying esophagus after the administration of metoclopramide.

(Slide) These are esophageal motility studies done prior to the administration of metoclopramide.

(Slide) This shows (slide) organized, good-quality, primary contractions of the esophagus, progression and good pressures.

Now, this particular patient did very well. Unfortunately, in patients treated with a primary low-pressure problem of peristaltic action in the esophagus, we have had objective findings, as you see here, that metoclopramide is very beneficial in restoring tone and peristalsis to the esophagus, but we have been dismayed to have our pH probe show reflux in the face of these good peristaltic contractions. Possibly because of the short duration of metoclopramide—only 45 minutes or so per dose—the patients do not have benefit for reflux symptoms. For problems as described by Dr. McClelland, we've been very pleased with it.

One of the things we have noticed, though, Dr. McClelland, is that two patients who have come back after two to six months have required a second run with metoclopramide and have had similar findings to the initial appearance of their symptoms; I suspect that you will have some too, eventually.

Dr. Paul H. Jordan (Houston, Texas): Our experience with this drug for this purpose has been unsatisfactory.

I don't know why there is this difference, but on repetitive doses to patients who would not empty their stomach, who had had vagotomy and antrectomy and who did have a patent stoma—this drug did not contract the stomach and contribute to gastric emptying.

The use of the drug for strengthening the lower esophageal sphincter—has also not been found to be helpful, either.

I would like to ask Dr. McClelland one question; the company brought this drug before the FDA and recommended its approval for a whole host of things. I wonder what the current status of this application is. Is the request for approval by the FDA still active and if so for what indications?

Dr. Robert N. McClelland (Closing discussion): I believe that it is very probable that failure to obtain good results with metoclopramide in the treatment of gastric atony referred to by some of the discussants may chiefly relate to the condition of the stomach when this agent is used. As you recall, none of our patients who developed postoperative gastric atony had undergone surgical treatment because of chronic pyloric obstruction; instead, all had been operated upon because of hemorrhage and/or intractable pain due to peptic ulcer disease. We and other surgeons have found that there is an inordinate incidence of persistent gastric atony when a vagotomy is performed in the presence of chronic, high grade pyloric obstruction which has caused severe gastric decompensation characterized by marked dilation and edema of the stomach. For this reason, we continue to treat patients with significant gastric decompensation due to chronic pyloric obstruction, by performing two-thirds subtotal gastric resection without vagotomy in relatively better risk patients, or by performing gastroenterostomy without vagotomy in elderly, poor-risk patients with high grade pyloric obstruction.

During the period of the study reported in our paper, several patients with severe chronic pyloric obstruction had gastric surgical procedures without vagotomies and none of these patients developed persistent postoperative gastric atony. I suspect that a number of these chronically obstructed patients would have developed persistent gastric atony if they had undergone vagotomy in conjunction with a resection or drainage procedure and if this had occurred I think metoclopramide would have been much less effective in relieving atony in these patients because of their grossly decompensated, dilated and edematous stomachs. Perhaps those who find metoclopramide not to be as effective as we do in the treatment of gastric atony have most often used this agent to treat atony occurring after vagotomy in patients with severe, chronic pyloric obstruction. This may explain the discrepant results obtained with metoclopramide referred to by the discussants.

Before our use of metoclopramide we employed Urecholine in the treatment of gastric atony, but we have found metoclopramide to be much more effective and to cause far fewer side effects than Urecholine.

Dr. Way, we did not study the possible effects of central intravenous hyperalimentation on gastric atony in our patients; however, the atonic state was well established before hyperalimentation was begun and it did not seem that this type of important nutritional support aggravated gastric atony in our patients. It definitely did not impair their response to metoclopramide.

At present, the FDA has not released metoclopramide for general usage. There is some concern by the FDA about the tendency of metoclopramide to elevate serum prolactin levels when used for long periods, with resultant concern about the effect of this elevation on breast cancer. However, the degree of prolactin elevation is little or no more than is caused by several phenothiazines that have been on the market for a long time. It is hoped that metoclopramide will soon be released for general usage, at least for short term use in the treatment of acute postoperative gastric atony.

Surgical Correction of Congenital Heart Disease in the Adult:

Experience With 139 Patients

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Patients over 18 years of age who have undergone a surgical correction of a congenital cardiac malformation during the period 1968 through 1977 have been reviewed. Those patients with calcific aortic stenosis which was thought, but not proved, to have arisen in a congenitally malformed aortic valve, were excluded from the review. Patients with cystic medial necrosis of the aorta were similarly excluded. There were 139 patients in the series (age range from 18 years to 67 years). The most common defects were those involving the intra-atrial septum and the related great veins, 50%. Abnormalities involving the great arteries including patent ductus arteriosus and coarctation of the aorta accounted for 19%. Common defects of conal development including ventricular septal defects and Tetralogy of Fallot malformations accounted for 15%. Valvular abnormalities including pulmonic stenosis, aortic valve abnormalities and Ebstein's malformation of tricuspid valve accounted for 11.5%. Complex congenital malformations were relatively uncommon, 4%. There were two patients with a combination of acquired and congenital heart disease. There were two operative deaths in the series, both occurring in patients with complex forms of congenital heart disease (multiple ventricular septal defects, double outlet right ventricle). There were two additional postoperative hospital deaths, one occurring following repair of an atrial septal defect from massive pulmonary embolus, and another occurring six weeks following a Fontan procedure performed for tricuspid atresia. Thus, the hospital mortality for the series was 2.9%. This reviewed series reveals the incidence of operable congenital heart defects appearing in an adult cardiac surgical practice and demonstrates that surgical repair can be accomplished with a satisfactory low mortality rate.

THE SURGICAL MANAGEMENT of congenital malformations of the heart is primarily a pediatric problem. A few patients, however, with congenital heart disease remain unattended or undetected until adult life. Furthermore, palliative operations performed in infancy or childhood occasionally sustain satisfactory central circulatory function until early adulthood. Recent advances in the management of congenital malformations of the heart have led to a progressive abandonment of palliative procedures in favor of corrective operations. The technical complexities of these advances has led to the suggestion that the surgical management of congenital heart disease should be in the hands of cardiac surgeons with special training, and not be an occasional effort by those principally involved in the management of acquired heart disease. A corresponding division of labor between adult and pediatric cardiologists has already existed for some time.

At Washington University of St. Louis, where the authors practice, the Department of Cardiothoracic Surgery is responsible for both pediatric and adult cardiac surgery. Without exception, pediatric referrals are made through a group of pediatric cardiologists practicing at the St. Louis Children's Hospital, whereas adult referrals are made principally by private practicing internists and cardiologists, who refer to or practice at the Barnes Hospital. In an effort to determine the incidence and the nature of patients with congenital cardiac malformations who present for surgical correction, but who are not referred by a pediatric cardiologist, we have examined our records from 1968 through 1977. Since all of the operations performed on adult patients with congenital cardiac malformations were performed or supervised by surgeons with a large amount of experience in the management of congenital malformations in the pediatric age group, we have also attempted to determine from our experience what results can be

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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produced and should be expected in operations whenever the correction of congenital malformations of the heart are undertaken in adult patients. This report is a result of these investigations. The age of 18 years was arbitrarily chosen to divide adults from pediatric patients. It is recognized that certain adolescents between the ages of 14 and 18 are variably referred by a pediatric cardiologist, an adult cardiologist or a private practicing internist. For the few patients between the ages of 14 and 18 however, a review of the records did not always clarify the route of referral, and for that reason, the arbitrary age of 18 was chosen as a separation point.

Materials and Methods

Records of 139 patients who were operated upon for the correction of congenital malformations of the heart and who were over the age of 18 were reviewed. This number represents approximately 6% of all adult heart operations during the same period, and represents 12% of operations performed for congenital heart disease. A number of patients with calcific aortic stenosis, who were thought, but not proved, to have congenital malformations of the aortic valve were excluded from the study. Similarly, patients with cystic medial necrosis of the aorta which is known to be a genetic disorder were excluded from the study In the group of 139 patients, 11 patients had had previous palliative surgical procedures, and three patients had residual malformations after an earlier attempt at corrective surgery. One hundred twenty five patients or 90% of the group were first considered as surgical candidates as adults. There were 56 males and 83 females, ranging in age from 18 to 67 years (Fig. 1), with a mean age at the time of surgery of 34.4 years. Telephone interviews were carried out to complete the follow-up of certain subsets of patients within the group of 139 patients.

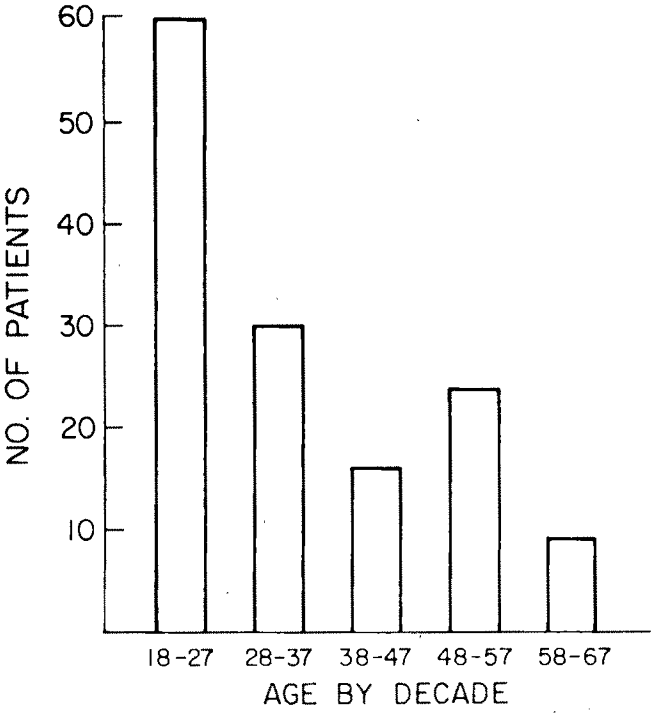

FIG. 1. Age distribution of 139 adult patients with repaired congenital heart disease.

Results

Of 139 patients operated upon as adults for the correction of congenital malformations of the heart, there were four hospital deaths. One hundred thirty five patients were discharged from the hospital. Three hospital deaths occurred during or following corrections of complex congenital malformations of the heart, and one followed a simple suture closure of an ostium secundum atrial septal defect performed in 1971. The incidence of specific malformations encountered is shown in Table 1. Ostium secundum atrial septal defects were repaired in 58 adults, accounting for 42% of the series. There were two patients with sinus venosus type atrial septal defects, four patients with anomalies of pulmonary venous drainage, three patients with partial type atrioventricular canal defects and two patients with cavo-atrial fistulas following a prior closure of an atrial septal defect. Thus, one-half of the adult patients with congenital malformations of the heart had either defects

TABLE 1. *Incidence (Operated Congenital Heart Disease in Adults)*

Area	Number	% Total
Atrial Abnormalities		
Ostium secundum atrial septal defect	58	42%
Sinus venosus atrial septal defect	2	1.5%
Caval-atrial fistula following prior atrial defect closure	2	1.5%
Atrioventricular canal (partial type)	3	2%
Anomalous pulmonary venous drainage	4	3%
Total	69	50%
Great Vessel Abnormalities		
Persistent patent ductus arteriosus	9	6%
Coarctation of the aorta	18	13%
Total	27	19%
Common Conal Defects		
Ventricular septal defect	10	7%
Tetralogy of fallot	11	8%
Total	21	15%
Pulmonic Stenosis	7	5%
Aortic Valve Abnormalities	7	5%
Ebstein's Malformation of the Tricuspid Valve	1	0.5%
Complex Congenital Malformation	5	4%
Congenital Malformations Associated With Acquired Valvular Heart Disease	2	1.5%
Total	139	100%

of the intra-atrial septum or anomalies of the related draining veins. Congenital anomalies of the great vessels were encountered in 19% of the series, with persistency of the ductus arteriosus noted in nine patients, and coarctation of the aorta in 18 patients. Common defects of conal development accounted for 15% of the series, with ten patients having isolated ventricular septal defects and 11 patients having Tetralogy of Fallot malformations. There were seven patients (5%) with isolated pulmonic stenosis, seven patients (5%) with congenital aortic valve or left ventricular outflow tract abnormalities, and five patients (4%) with complex congenital malformations. Two patients appeared with a combination of congenital malformations and acquired valvular heart disease. One patient had Ebstein's malformation of the tricuspid valve.

Ostium Secundum Atrial Septal Defect

Ostium secundum type atrial septal defect was repaired in 45 females and 13 males. The age range was from 18 to 67 with a mean age of 40 (Fig. 2). Eighteen percent of the patients with this malformation were asymptomatic, but were referred for surgery following detection of an abnormal cardiac silhouette or a cardiac murmur and confirmation of the defect by cardiac catheterization. Three percent of the patients had experienced chest pain, 5% fatigue, 31% dyspnea with exercise, 3% cardiac palpitations, 31% gave a history of congestive failure, 3% had dizziness of near syncope, and 5% had a history suggesting paradoxical emboli. Cardiac catheterizations were performed in all patients, 26% of patients had a preoperative pulmonary arterial arterial pressure in excess of 25 TORR. In 48% of patients, the ratio of pulmonary blood flow to systemic blood flow was in excess of 2.5

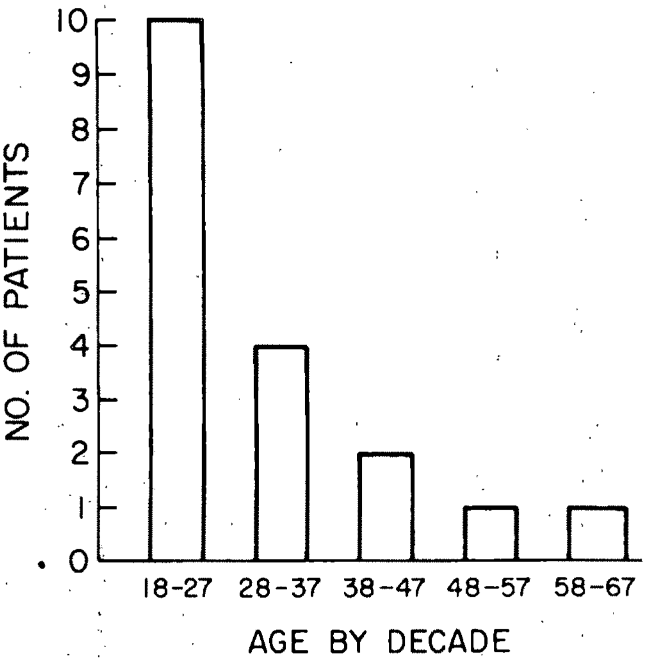

FIG. 2. Age distribution of 18 adult patients with repaired coarctation of the aorta.

All repairs were done with a formal cardiopulmonary bypass. Technique of repair was a primary suture closure of the defect in 67% and closure of the defect with a prosthetic patch in 33%. Cardiac arrhythmias were a common postoperative complication. In 53% of the patients, no postoperative arrhythmia was documented. However, in 5%, there was an episode of paroxysmal atrial tachycardia, in 5% of an episode of atrial flutter, and 16% an episode of atrial fibrillation. Atrial extrasystoles were noted in 7% of the postoperative population. Premature ventricular contractions were noted in 9%, and a nodal rhythm was recorded on at least one instance in 16%. Postoperative left ventricular failure was an uncommon complication. Despite the fact that congestive failure had been noted as a preoperative symptom in 31% of patients, anticongestive therapy was required in only 9% postoperatively. There were three patients with documented episodes of postoperative emboli requiring catheter embolectomy from the femoral vessels. This represents an incidence of 5%. There was no documented incidence of cerebral embolization. There was a single postoperative death accounting for a mortality of 2% in the series of repaired ostium secundum atrial septal defects. This death occurred in 1971 in a 31-year-old female, following suture repair of an inter-atrial ostium secundum atrial septal defect. Her postoperative course was complicated by frequent and severe ventricular arrhythmias which failed to respond to a variety of anti-arrhythmic agents. An episode of ventricular fibrillation occurred on the third postoperative day. Autopsy study revealed multiple pulmonary emboli. Follow-up of the group of 57 patients is incomplete, but we are unaware of any late deaths or significant complications.

Anomalous Pulmonary Venous Drainage

Four patients with anomalous venous drainage from one lung were encountered. In a 21-year-old male, the veins from the left lung entered the coronary sinus. Repair involved excision of the superior wall of the coronary sinus, excision of the adjacent inter-atrial septum, and prosthetic patch closure to include the surgically created intra-atrial septal defect, and the ostium of the coronary sinus. A 62-year-old male, who had had an inter-atrial septal defect closed in the early years of open heart surgery was found to have the right pulmonary veins draining into the right atrium. Repair

TABLE 2. *Persistently Patent Ductus Arteriosus**

Age, Sex	Preoperative PAP (Torr)	Shunt	Calcium	Operative Technique
29/F	33	1.4:1	0	Division between clamps
18/F	20	"Small"	0	Division between clamps
23/F	25	1.7:1	0	Division between clamps
21/M	23	1.2:1	0	Division between clamps
18/F	18	Not calculated	0	Division between clamps
56/F	26	1.8:1	++	Divided after isolation within Potts-Smith clamp
27/M	70	2.9:1	0	Divided after isolation within Potts-Smith clamp
18/F	25	2:1	0	Divided after isolation within Potts-Smith clamp
55/F	80	2.3:1	++++	Divided after isolation on cardiopulmonary bypass with cannulation of aorta above and below ductus

* Mortality = 0.

involved excision of a portion of the inter-atrial septum with prosthetic patch reconstruction and repositioning of the atrial septum. A 26-year-old-male with an ostium secundum atrial septal defect in combination with anomalous drainage of the right pulmonary veins into the right atrium was repaired by prosthetic reconstruction and repositioning of the atrial septum. A 32-year-old male with a "scimitar syndrome" with the right pulmonary veins draining into the inferior vena cava, was repaired with a complex operation in which the anomalous pulmonary vein was detached from the inferior vena cava and sewn into the right atrial wall. An inter-atrial septal defect was created, and a prosthetic tunnel arranged within the right atrial chamber to connect the atrial septal defect and the anastomotic site between the pulmonary vein and the right atrial wall. There were no hospital deaths in this group of patients, and all four patients remained well and without symptoms.

Sinus Venosus Atrial Septal Defect

Sinus venosus atrial septal defect was encountered in two adult male patients. Repair was performed by inserting a prosthetic patch into the inter-atrial defect, with realignment of that portion of the septum so as to direct the anomalous veins beneath it in combination with prosthetic reconstruction and enlargement of the superior caval-right atrial junction. There were no hospital deaths and both patients remain well.

Partial Atrio-Ventricularis Communis

Atrio-ventricular canal defects were encountered in three adult female patients. In all cases, the anomaly was of the partial form. No patients with complete atrio-ventricular canal defects who were not established Eisenmenger's have been encountered. This series of three patients included a woman and her daughter with identical defects. A third patient had an associated pulmonary stenosis. Repair of the defect was standard with suture closure of the mitral cleft and repair of the ostium primum type atrial septal defect, with a composite patch of pericardium fixed to Teflon® felt. This composite patch is placed so that the pericardium is on the left atrial side, and is designed to eliminate hemolysis in the event of any mitral regurgitation. For many years, we have used such a patch for the repair of this type of defect. There were no deaths in this series of three patients, and all three patients remain well.

Inferior Vena Cava to Left Atrial Fistula

This anomaly was encountered in two patients. It is iatrogenic and results from an improperly repaired fossa ovalis type ostium atrial septal defect. Both patients had had atrial septal defects closed in the early years of open heart surgery. The fistula creates severe cyanosis. Repair requires re-opening of the inter-atrial septum through the fistula and a proper prosthetic reconstruction of the inter-atrial septum. Venous cannulation from the leg was required in both cases. There were no deaths in the series, and both patients remain well.

Persistently Patent Ductus Arteriosus

Persistent patency of the ductus arteriosus was encountered in seven female adult patients, and two male adult patients (Table 2). Severe pulmonary arterial hypertension was present in only two of the nine patients. Calcification of the ductus was noted in a 56-year-old female and a 55-year-old female. The persistently patent ductus was divided in all adult cases. In five instances, this division was between ductus clamps, and in three instances, the aortic end of the ductus was isolated within a Potts-Smith aortic clamp. In one instance, the ductus was isolated between aortic cross clamps after the institution of a formal cardiopulmonary bypass, with cannulation of the aorta above and below the ductus area,

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and with venous cannulation of the right ventricular outflow tract. There were no hospital deaths in this group, and all patients at most recent follow-up were asymptomatic.

Coarctation of the Aorta

Coarctation of the aorta was encountered in 18 adult patients. The age range was 18–59 years with a mean age of 31.4 (Fig. 3). In 17 of 18 patients the coarctation was an isolated malformation. In one patient, aged 33, it was associated with a persistently patent ductus and a small ventricular septal defect. In 15 patients, a juxtaductal coarctation was excised, and end-to-end aortic anastomosis performed. In two patients, the coarctate segment was long, and following excision, a tubular dacron prosthetic segment was inserted. In one patient, the coarctation involved the transverse aorta between the left common carotid artery and the left subclavian artery. A prosthetic bypass between the ascending aorta and the descending thoracic aorta was performed. There was no hospital mortality in this series of patients.

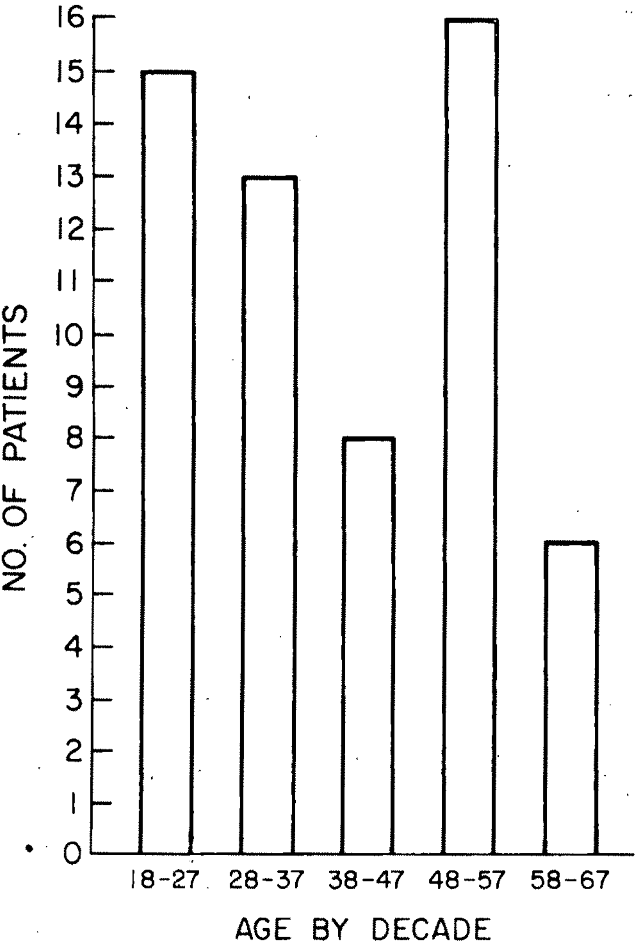

FIG. 3. Age distribution of 58 adult patients with repaired ostium secundum atrial septal defects.

Follow-up study of this group of 18 patients indicate that 13 patients are normotensive, but that five patients have remained hypertensive to a degree that antihypertensive medication is essential for control.

Ventricular Septal Defect

Ten adult patients were operated upon to close ventricular septal defects (Table 3). In four male patients, a small ventricular septal defect was closed by direct suture technique. In none of these patients was there a significant elevation of the pulmonary arterial pressure. Left to right shunts were relatively small except for one patient who had an associated atrial septal defect which was also closed by suture technique. Two patients in this series were operated upon for severe aortic insufficiency. A 45-year-old female with pulmonary arterial hypertension was thought to have aortic insufficiency with an associated ventricular septal defect, but at the time of surgery, was found to have a ventricular septal defect with an associated sinus of Valsalva fistula. At operation, the ventricular septal defect was sutured, the sinus of Valsalva fistula was repaired, and a plastic reconstruction of the aortic valve was performed to provide a proper suspension of the leaflets. A 22-year-old male with no detectable ventricular septal defect at cardiac catheterization was found to have a ventricular septal defect with aortic insufficiency. In this unusual case, the right leaflet of the aortic valve had prolapsed through a moderate sized ventricular septal defect, and had become affixed to the margins of the defect by calcification. The valve leaflet was dissected out of the ventricular septal defect, and the defect was closed with a patch through a ventriculotomy. Debridement, and a resuspension of the right leaflet was performed. This patient, however, had severe persistent aortic insufficiency in the postoperative period and required a second operation, at which time the aortic valve was excised and replaced with a prosthetic aortic valve.

Four patients had large ventricular septal defects, with large left to right shunts, and were symptomatic. One of these was thought preoperatively to be a Tetralogy malformation, but at operation proved to be a large ventricular septal defect with associated valvular pulmonic stenosis. Another patient had an L-transposition of the great arteries. In all four of these cases, the ventricular septal defect was closed by the insertion of a prosthetic Dacron patch. One patient in this series was of considerable interest; a 49-year-old female with severe pulmonary arterial hypertension. At the time of surgery, she had a ventricular septal defect which measured more than 2 cm in diameter in the membranous portion of the inter-ventricular septum. There was no

TABLE 3. *Ventricular Septal Defects**

Age, Sex	Preoperative RVP	Shunt	Indication	Type Repair	Postoperative RVP
38/M	31	1.6:1	Cardiomegaly	Direct suture closure	Normal
22/M	22	1.3:1	"to buy insurance"	Direct suture closure	Normal
27/M	30	1.6:1	Cardiomegaly	Direct suture closure	Normal
19/M	35	3.1:1	Cardiomegaly with ASD	Direct suture closure of both ASD and VSD	Normal
45/F	80	1.6:1	Aortic insufficiency	Suture of VSD and closure of sinus Valsalva fistula with repair of prolapse of aortic valve	Normal
21/F	38	2.3:1	Atrial fibrillation with cerebral emboli	Prosthetic patch closure	Normal
49/F	108	3.6:1	Dyspnea	Prosthetic patch closure	35
19/M	100	2.6:1	L-Transposition with VSD	Prosthetic patch closure	50
32/F	72	2.8:1	Thought to have Tetralogy	Prosthetic patch closure and pulmonary valvotomy	40
22/M	25	None detected at cath.	Cardiomegaly with AI	Prosthetic patch closure of VSD aortic valvuloplasty, secondary aortic valve replacement.	Normal

* Mortality = 0.

evidence of obstruction anywhere in the right side of the heart. Closure of this ventricular septal defect produced an immediate fall in the pulmonary artery pressure to a normal range. Failure of this very large defect to produce an Eisenmenger reaction for a 49-year period is most unusual and unexplained. There were no hospital deaths in this series of ten patients, no incidence of surgically produced heart block, and no evidence in the postoperative period of residual ventricular septal defect. Right ventricular pressures were reduced to normal or near-normal in all cases.

Tetralogy of Fallot

Eleven adult patients underwent repair of Tetralogy of Fallot malformations during this study (Table 4). The age range in the series was large with one patient being in the fourth, one in the fifth, and one in the sixth decade of life. All patients had cyanosis. Six of the 11 patients had had palliative procedures performed in childhood. Three had had Blalock-Taussig shunts, two had had Brock type blind infundibulectomies, and one had had a Potts anastomosis performed. The duration of palliation in these patients was long, varying from 17 to 24 years. It is of interest that among the five patients who had had no palliative procedure were the three oldest patients in the series. One of these patients suffered from chronic schizophrenia, and had previously not been thought to be a candidate for repair of his congenital heart malformation. Another was a deaf mute who similarly was thought ineligible for a cardiac operation, and the third was a 46-year-old mother who agreed to

TABLE 4. *Tetralogy of Fallot**

Age, Sex	Previous Surgery	Duration of Palliation (Yrs.)	Outflow Tract Reconstruction	Postoperative RV Pressure (Torr)
21/M	Brock	17	—	40
24/F	Left Blalock-Taussig	20	—	30
22/M	Brock	17	—	50
27/F	—	—	—	Not measured
34/F	Left Blalock-Taussig	24	Prosthetic patch	60
24/M	—	—	Prosthetic patch	30
24/F	Potts	18	Prosthetic patch	40
46/F	—	—	Prosthetic patch	50
62/M	—	—	Prosthetic patch	40
25/F	Right Blalock-Taussig	19	Tubular valved homograft	50
51/M	—	—	Hancock prosthesis	25

* Mortality = 0.

have the repair following the successful correction of a Tetralogy malformation in her teenage son.

The surgical procedure involved interruption of previously constructed shunts, infundibulectomy and ventricular septal defect closure in all patients. In four patients, it was possible to complete the repair without reconstructing the infundibular portion of the right ventricle. In five patients, a prosthetic patch was used to enlarge the outflow tract portion of the right ventricle, and the proximal portion of the pulmonary artery. In one patient with acquired atresia of the right ventricular outflow, an extensive reconstruction of the outflow tract was performed by inserting a tubular valved homograft. It is of interest that this patient is now seven years postoperative, and since the operation has successfully completed two pregnancies. Another patient required insertion of a tubular prosthesis containing a porcine valve to bridge the pulmonary valve annulus. This was done because of an anomalous distribution of the left coronary artery. There were no hospital deaths in this series of 11 patients. A satisfactory reduction of right ventricular pressure was achieved, and on postoperative testing, there was no evidence of residual shunting across the ventricular septum. All 11 patients have been followed for a period of six months to nine years. Ten patients remain asymptomatic with a normal exercise tolerance. A patient repaired at age 62 died three years and four months following surgical repair. Cause of death is unknown.

Pulmonic Stenosis

Pulmonic stenosis was encountered in five female adult patients and two male adult patients. In five of the seven patients, the defect was isolated valvular pulmonic stenosis. These patients underwent open commissurotomy. In one patient, valvular pulmonic stenosis was associated with an atrial septal defect that was closed at the time of the pulmonary valve commissurotomy. The seventh patient had infundibular pulmonary stenosis, which had been, in childhood, associated with a proven ventricular septal defect, but this ventricular septal defect had closed. It is recognized that this patient falls into the category of defects of conal development, but for purposes of simplification, has been classified as pulmonic stenosis. The operation performed was a simple infundibulectomy to relieve the obstruction. Although a considerable reduction of the gradient between the right ventricle and the pulmonary artery was achieved in all patients, high gradients were left at the end of the operation in four of these patients. It has been our policy not to perform infundibulectomies for work hypertrophy of the right ventricular outflow tract since this is known to resolve following the relief of the valvular obstruction. There were no deaths in this series of patients, and all patients remain asymptomatic at the present time.

Abnormalities of the Aortic Valve and Left Ventricular Outflow Tract

All patients in this series were male (Table 5). Two patients had membranous subvalvular aortic stenosis treated by resection of the obstructing fibrous membrane. Two patients had had previous commissurotomies for aortic valve stenosis performed 11 and 16 years previously. In both cases, the deformed aortic valve was excised and replaced with an aortic valve prosthesis. One patient at the age of 19 had a commissurotomy performed for the first time for relief of valvular aortic stenosis, and another 22-year-old had a prosthetic valve replacement for what was clearly congenital aortic stenosis. A final patient had a combination of coarctation of the aorta, and aortic valve disease which provided for both stenosis and aortic insufficiency. The aortic insufficiency was severe. This patient was treated by replacement of the deformed aortic valve with a prosthesis. Relief of obstruction was obtained in all cases. There were no hospital deaths in this series.

Ebstein's Malformation of the Tricuspid Valve

A single adult patient with Ebstein's malformation of the tricuspid valve was operated on during the time period of the study. This patient was 45 years old at the time of operation. He was severely cyanotic with a hematocrit of 80%, and had suffered cerebral vascular thrombosis with good resolution of temporary neurological deficits. He had been treated with venesections for the relief of his polycythemia. This effort eventually produced a shock state. An emergency operation was performed following the treatment of shock. The tricuspid valve was replaced with a prosthesis, inserting the prosthesis above the coronary sinus; an atrial septal defect was closed. This patient remains well and asymptomatic five years following surgery.

Complex Forms of Congenital Heart Disease

Five adults with complex forms of congenital heart disease were operated upon during this study. In this category a high hospital mortality occurred. There were three hospital deaths among the five patients, accounting for a mortality of 60%. The group included a 22-year-old male with tricuspid atresia, treated in childhood with a construction of a Blalock-Taussig shunt. At the time of his operation, he had atrial fibrillation and congestive heart failure. A modified Fontan procedure was performed, dismantling the Blalock-Taussig

TABLE 5. *Aortic Valve Abnormalities**

Age, Sex	Diagnosis	Previous Surgery	Preoperative Gradient (Torr)	Preoperative Gradient (Torr)	Procedure
37/M	Subvalvular AS	—	100	10	Resection of membraneous subaortic stenosis
26/M	Subvalvular AS	—	65	5	Excision of fibrous band beneath AV
25/M	Severe AI	16 years post commissurotomy for valvular AS	0	—	Insertion of a prosthetic aortic valve
18/M	Valvular AS	11 years post commissurotomy for valvular AS	90	—	Insertion of a prosthetic aortic valve
19/M	Valvular AS	—	80	Not measured	Aortic valvotomy
22/M	Valvular AS	—	80	Not measured	Insertion of a prosthetic aortic valve
49/M	Coarctation of aorta with bicuspid AV and severe AI	—	Not measured	—	Insertion of a prosthetic aortic valve

* Mortality = 0.

shunt, isolating the right atrium between valves and inserting a prosthesis from the right atrium to the pulmonary artery which had been detached from the heart. The patient had an initial relief of cyanosis, but died six weeks following his operation. At autopsy examination, there was thrombosis of the inferior vena cava, the right atrium and the pulmonary artery. A 24-year-old female with an S.D.D. double outlet right ventricle with subpulmonic stenosis had an injury to the mitral valve produced at the time of repair. Prosthetic mitral valve replacement was performed. She died in the early postoperative period with left ventricular failure. A 20-year-old-female had a Tetralogy type defect of the infundibulum associated with multiple muscular ventricular septal defects, and a single pulmonary artery; a Blalock-Taussig shunt had been constructed in childhood. Following repair of this complex defect, there was evidence of severe residual interventricular shunting. This patient died in the operating room. Two other patients, ages 19 and 38 had successful repairs of S.D.D. double outlet right ventricles. In both cases, there was severe subpulmonic stenosis, and in one case, the ventricular septal defect was related to the aortic valve while in the other, it was related to the pulmonary valve.

Congenital Heart Coexisting with Acquired Valvular Heart Disease

Two patients were encountered who had congenital heart disease and associated acquired valvular heart disease. A 48-year-old female was operated on in 1969 for the ligation of a ductus arteriosus, the closure of an ostium secundum atrial septal defect and for prosthetic replacement of the tricuspid and mitral valve which were involved with rheumatic valvulitis. This patient remained well until 1977, when she developed an episode of endocarditis involving the prostheses. She had increasingly severe congestive heart failure, and by this time, had developed aortic insufficiency. She was reoperated upon; the mitral and tricuspid prostheses were removed, and three porcine bioprostheses were used to replace the aortic, the mitral and the tricuspid valves. This patient remains well a year later. A second patient, age 29, was operated on in 1973 for severe aortic insufficiency complicating bacterial aortic valvulitis. At the time of aortic valve replacement, a large ostium secundum atrial septal defect was closed by direct suture. This patient was well until 1977, when she developed evidence of aortic insufficiency, and was found to have a dehiscence of the aortic valve prosthesis. A reoperation was performed. Cultures from the valve grew bacteria. The infected prosthesis was replaced with a porcine stented bioprosthesis, and at the same time, the mitral valve which was also involved with endocarditis and which had become insufficient was replaced with a porcine bioprosthesis. Although her initial postoperative course was satisfactory, and despite intensive antibiotic therapy over a prolonged period of time, her infection was never controlled and she died of uncontrolled sepsis nine months following the second cardiac operation.

Late Mortality

Follow-up on this series of 139 patients with congenital heart disease operated over a ten-year period is incomplete; a number of the patients, after periods of follow-up, were judged to have normal central circulations and are no longer followed. An attempt made to contact patients by telephone produced a complete follow-up for certain subgroups, but not for the complete series. We are, however, aware of three late deaths. Two of these occurred in patients in whom prosthetic valves had been implanted. One such late mortality is described above and occurred as a result of uncontrolled sepsis on the patient's native aortic valve and subsequently on two inserted prostheses. Another late death occurred in a patient with coarctation of the aorta, and associated aortic valve insufficiency and stenosis. This patient was treated by the insertion of an aortic valve prosthesis. His postoperative course was uncomplicated. He was brought to the hospital seven months following his surgery with a massive hemoptysis and cardiac arrest. Permission for autopsy examination could not be obtained. A third late death occurred three years and four months following repair of a Tetralogy malformation in a 62-year-old-male. The cause of death is unknown.

Discussion

Previously reported series of adult patients with congenital heart disease have confirmed that operative therapy of this group of patients can be performed with a low mortality and morbidity, and with excellent early and late results. Gerbode and associates[5] in 1964 reported a series of 190 patients with 16 hospital deaths (8.4%). Coles and associates[4] reported in 1964 from London, Ontario a series of 25 patients with two hospital deaths (4%). Johnson and his associates[6] reported in 1966 a series of 41 patients treated at Marquette University, with one death (2.4%). Cohn and Collins[3] reported in 1973 a series of 54 patients from Peter Bent Brigham Hospital with no hospital deaths, and Bekoe and associates[1] reported in 1975 a series of 50 such patients treated at the Alleghany General Hospital with no deaths. The largest series of adult patients with congenital heart disease was reported by Kay and associates[7] from the Medical College of Wisconsin in 1976. Their report provided a detailed study of 205 patients. There were seven hospital deaths (3%). All of these series included patients with patent ductus, coarctation, atrial septal defects, ventricular septal defects and Tetralogy malformations. Several series included a few patients with Ebstein's malformation of the tricuspid valve or coronary artery anomalies. Our series, which includes 139 patients, shows a hospital mortality of four deaths (2.9%). However, in our series, there was a small group of patients operated upon for complex congenital malformations of the heart, and two patients with a combination of congenital malformations and acquired valvular heart disease. Such patients have not been previously included in reported series. The mortality in our series was principally associated with patients who had complex congenital malformations and who had survived to adulthood with previously performed palliative procedures. If this group of patients were eliminated from our series, the overall hospital mortality for the series would be one patient or 0.75%.

At this time there is no comparable data on congenital heart defects repaired in infancy or childhood and those repaired in adulthood. Our experience suggests that the Tetralogy heart, properly repaired, is a well functioning heart, whether this repair is carried out in infancy, childhood or adulthood. Although repair of coarctation of the aorta in adults has been effective in reducing the level of blood pressure in the upper extremities, it is now recognized that the history of patients with repaired coarctation of the aorta, whether this is done in infancy, childhood or adulthood, does not conform to that of the normal population.[8] Defects which produce excessive pulmonary blood flow at high pressure, such as persistent patency of the ductus and ventricular septal defects, produce a progressive destruction of the pulmonary vasculature. There is now evidence[2] that shunts which provide an adequate stimulus for the development of pulmonary microvascular disease produce most of this pulmonary vascular destruction within the first few years of life. Thus, an appeal has been made to correct ventricular septal defects and persistently patent ductus within the first few years of life. In our series of patients with persistently patent ductus, two patients already had well established pulmonary arterial hypertension, and seven had pulmonary blood flows which did not exceed more than twice the systemic blood flow. Though division of the ductus was accomplished safely in this group of patients, it remains unclear whether the operation had a beneficial effect in regard to life expectancy or the preservation of central circulatory function. In our series of ten adult patients with ventricular septal defect, three patients had small ventricular septal defects and small shunts, and it is possible that these may not have been of consequence in regard to central circulatory function or life expectancy. Two patients, however, had large shunts, with elevation of pulmonary artery pressure and the operations produced a reduction in the pulmonary artery pressure to normal levels. In the five remaining patients, the ventricular septal defect was associated with another cardiac malformation. The combination had produced symptomatology which was relieved by closure of the ventricular septal defect and correction of the associated malformation.

Both pulmonic stenosis and aortic stenosis which provide severe ventricular afterload are clear indications for operative intervention to restore and maintain ventricular performance. Defects of the inter-atrial septum and the related pulmonary and systemic veins are clearly the most commonly encountered congenital defects in adult patients. This is so because these abnormalities do not commonly produce symptoms until middle age. In our series, approximately 80% of the patients had symptoms related to a disturbance in central circulatory function. The most common of these was dyspnea with exercise and evidence of congestive heart failure. This was so despite the fact that only approximately 25 of the patients had an elevation of pulmonary artery pressure. Much of this symptomatology, we believe, was related to right ventricular diastolic overload and to pulmonary plethora. Both of these conditions, of course, are relieved by repair of the atrial shunt. On the other hand, although palpitation was an uncommon complaint before the operation, some sort of cardiac arrhythmia was documented in nearly half of the patients in the postoperative period. We are unaware of any study which proves that the repair of atrial defects encountered in adults produces a reduction in the incidence of supraventricular arrhythmias. We are similarly unaware of any study which demonstrates that repair of such defects in adulthood increases longevity. Nonetheless, our experience with this group of 69 patients indicates that in most instances, symptoms related to right ventricular diastolic overload and pulmonary plethora are relieved.

Technical advances in the management of cyanotic congenital heart disease have produced a diminution in the number of palliative shunts performed in favor of early corrective procedures. In addition, it is recognized that shunts performed in infancy should not be permitted to function over many years, but should be interrupted after relatively short intervals with a secondary corrective procedure. It is likely therefore that in the future, fewer patients will enter adulthood with cyanotic forms of congenital heart disease by virtue of a palliative procedure performed in infancy or childhood. At the same time, it is reasonable to speculate that many complex corrective operations for congenital heart disease now being performed in infancy and childhood will require secondary or tertiary operations. Such maneuvers as the construction of intra-atrial baffles, valve reconstruction and prosthetic reconstruction of the right ventricular outflow tract performed in infants are likely, in certain instances, to require enlarging procedures with growth. Such secondary procedures, however, will probably be required in childhood and the principal form of secondary or tertiary cardiac surgery in the adult population is likely to be in those who had valve reconstruction or replacements as part of their primary repair. Up to the present time, only a few patients with congenital aortic stenosis represent this category in our series.

In this series of 139 patients, only three adult patients (2%) required re-operation because of an improperly performed operation during childhood, and 11 patients (8%) survived to adulthood by virtue of a palliative procedure performed during childhood. Thus, a full 90% of adult patients referred for the management of congenital heart disease had their condition unrecognized or unattended during infancy and childhood. With rare exceptions, this group of patients has been referred for management by private internists and cardiologists not closely associated with any pediatric cardiology group. Referral of these patients in the future is likely to be to surgical groups primarily involved in the management of acquired heart disease rather than to groups specializing in the management of congenital heart disease. The repeated demonstration that excellent results can be obtained for this group of adult patients with congenital heart disease with a low morbidity and mortality remains a potent argument for the continued training of all cardiac surgeons in the special techniques required for the management of congenital forms of cardiac disease.

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Discussion

Dr. Denton A. Cooley (Houston, Texas): We have long been interested in surgical correction of congenital cardiac anomalies in adults and, stimulated by the report from Barnes Hospital, I have reviewed our 25-year experience at the Texas Heart Institute with patients more than 18 years of age.

(Slide) A total of 2063 patients underwent operation, with 147, or 7.1%, expiring during the first 30 days. The most common diagnosis was secundum atrial septal defect—488 cases, with seven deaths, or 7.1%. In order of decreasing frequency were aortic stenosis, coarctation, ventricular septal defect, tetralogy of Fallot, IHSS and patent ductus arteriosus. I noticed that Dr. Leidenfrost excluded IHSS from the congenital group. The oldest patient who had IHSS was 81-years-old and survived operation.

(Slide) The remainder of cases had pulmonic stenosis, ASD primum, ASD sinus venosus, coronary fistula, dextrotransposition of the great arteries, common atrium and a miscellaneous group. 632 patients, or 30% of the total, had various types of correctable ASD, including ostium primum with cleft mitral valve.

Ages of the oldest patients are rather remarkable. For example, a 73-year-old man with cyanotic tetralogy of Fallot survived, as did a 77-year-old ASD, a 73-year-old ductus and a 69-year-old ASD primum with cleft mitral valve. In fact, among the oldest patients in each category, death resulted in only two, a 69-year-old patient with coarctation and a 75-year-old woman with an angiomatous fistula between the right coronary artery and main pulmonary artery. Both were in intractable failure before operation, and both died on the second day after operation with complications related to coronary atherosclerosis.

We agree with the authors that congenital cardiac defects may be repaired during adulthood with an acceptably low morbidity and mortality. Age alone should not be the limiting factor in decisions regarding operability. The factors which determine operability are, in general, the same as for patients in the pediatric age group.

I have enjoyed the paper by Drs. Leidenfrost and Weldon and wish to emphasize the point which they have made, that we should maintain a broad and comprehensive training for cardiac surgeons, both in congenital and in acquired heart disease.

Dr. Frank Gerbode (San Francisco, California): I'd like to compliment Dr. Leidenfrost, particularly on the low mortality rate from operating upon these patients.

We have had an experience of approximately 200 such patients in San Francisco, and I was interested some years ago not so much in the technique of doing the operation, which, of course, is of primary interest to the surgeon, but why these patients took so long to get to the surgeons. The diagnosis and treatment of congenital heart disease has been well advertised, and the surgical techniques have been talked about now for about thirty years; yet here we have 2000 patients who escaped the rest of us and went to Texas, and another 137 who were done in St. Louis, and we had about 200 in our place. Why were they not operated upon earlier?

I think that many of them were treated under misdiagnoses. Some were completely overlooked. Of the ASD's, when I looked over our series, most of them had been treated for rheumatic heart disease or a functional murmur of one kind or another, and it was only when curiosity got the better of a particular physician that he sent them in for referral.

I think some patients were simply misdiagnosed from the very beginning, like the Japanese from Hawaii who went through the entire war, and all the fighting in northern Italy, and finally after the War had to have an employment chest film when he was about 25 years old, when it was apparent he had a figure of eight deformity; he had total anomalous venous return. He had become quite cyanotic. I could list perhaps fifteen or twenty similar delayed diagnoses of severe congenital heart disease.

One other thing that I would like to mention, if I may, is that the result of surgery is not always that great. I notice the authors said that all the patients were really improved. Well, in our experience, there are certain categories of patients that are not always improved. For example, we have several ASD's in middle age who went on to complete heart failure after the closure of the ASD. Their hearts were simply worn out from the shunt they had been carrying for so long. We have seen this in other congenital abnormalities as well.

Supra aortic coarctation of the aorta is another example where the operation is relatively straightforward for a cardiovascular surgeon. We have had two patients who died suddenly, months after the operation, from some sort of ventricular episode—probably ventricular tachycardia of ventricular fibrillation. I believe that in such cases the coronary circulation peripherally may have been altered pathologically from high pressure, requiring a high-pressure coronary circulation to keep the hearts going.

Dr. Paul A. Ebert (San Francisco, California): I rise to make several comments regarding the problem of the patient with congenital heart disease in adulthood and realize that natural selection plays a great role in these patients before they become available. As Dr. Gerbode mentioned, the problem often is that they have minimal symptoms prior to the time of presentation. Where the general surgeon so often sees these patients is during the course of other treatments—of cholecystitis or other ailments—as they age.

The question always comes—the patient will almost always deny the need for operation because of the lack of symptoms, and the point has to be emphasized that the congenital heart patient usually does not have many symptoms in this particular group until they develop tired ventricles. Consequently, our experience has been that even though survival is quite good, a large per cent do fail to show significant clinical improvement.

There are several points in the paper that are of interest. It's a very small number of patients that presented having had any history of bacterial endocarditis, even though they had lived for many years with complex anomalies. Generally speaking, these are the simpler forms of congenital heart disease, and, of course, if recognized, they should be repaired earlier.

There is also a need for continuing interest in this field, because there is certainly going to be an emerging group of patients who have had previous operations in infancy or younger childhood for more complex anomalies, who are subsequently going to present in adulthood for some other type of augmentation.

I would be interested to know if you have had similar experience with the long-term outcome of many of the patients that have undergone surgery.

Dr. George C. Kaiser (St. Louis, Missouri): This is a very nice series, with superb results, from our sister institution in St. Louis. A few years ago a report was published from Baltimore concerning the lack of resolution of hypertension following repair of coarctation in older individuals. This report also indicated that longevity was not increased after operative repair. I noticed that in two-thirds of the patients presented today, hypertension was reduced after coarctation repair. I wonder if Dr. Weldon would share with us his ideas about the appropriateness of operative management of coarctation of the aorta in the adult.

Dr. Clarence Schock Weldon (Closing discussion): There have been three or four previous reports on this subject. Dr. Gerbode's report was the first. All of these papers indicate that adult patients with congenital heart disease can be managed with excellent survival statistics. Of course, before a patient with congenital heart disease becomes an adult, there is a good bit of therapeutic and natural selection which takes place; thus, most of the patients who present with congenital heart disease as adults do not have high-risk-type malformations.

One of the points I would like to emphasize is that this group of patients becomes patients as adults because, by and large, they were previously unrecognized, or unattended. They were almost exclusively referred by doctors who do not ordinarily deal with congenital heart disease as a specialty. I suspect that as the population of patients with acquired heart disease disperses from academic centers, this group of patients is going to disperse with them. I therefore do think it is important that all people who are trained to do cardiac surgery continue to be trained to handle certain types of congenital cardiac malformation.

In the manuscript, we deal more completely with the follow-up of these patients. There have been three late deaths in the group. The patient who had had a septic aortic valve continued to infect a series of prostheses and finally died of uncontrolled sepsis four or five years after the initial operation. A patient who had had an aortic valve and a coarctation of the aorta died following a massive hemoptysis. The man who had had a tetralogy repair at the age of 62 died four or five years after his operation of causes which we have not been able to determine.

I think, in answer to several of the discussants, we don't really known a lot about what we do in regard to central circulatory function by repairing congenital heart disease in adults. This series, like other series does indicate that we do not always cure the hypertensive disease that complicates coarctation of the aorta. On the other hand, it is so that coarctation of the aorta repaired in children is sometimes complicated by the reappearance of hypertensive disease and that the incidence of hypertensive disease is greater than in a normal population. It does seem to be so that a tetralogy heart, well repaired, is a well-functioning heart, independent of the age at which the repair is done.

We didn't say that all of our patients were asymptomatic. We said that this was so for certain subgroups.

I think one of the big mysteries is what we should do to the pulmonary hypertensive disease that almost always complicates atrial septal defect and anomalous venous return if the patient gets old enough. The cause of this pulmonary hypertensive disease remains obscure, and it may or may not be related to the Eisenmenger reaction that complicates shunts from ductus or ventricular septal defects.

I don't think anyone knows how often closure of the atrial septal defect in patients with established pulmonary hypertension relieves the hypertension, how often it halts the progression of the hypertension and how often it has no effect on the hypertension. No one has studied these patients postoperatively to determine whether the pulmonary hypertension is arrested, whether it regresses or whether, indeed, in some instances, it continues to develop. I do think that we have evidence that we do improve symptomatology in older patients with atrial septal defects. Much of this symptomatology is erroneously called heart failure, but has to do with pulmonary plethora and with right ventricular diastolic overload, both of which are relieved by closing the atrial septal defect, whether the pulmonary hypertension is relieved or not.

Management of External Gastrointestinal Fistulas

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J. ENGLEBERT DUNPHY, M.D.

We analyzed the course of 186 patients with external gastrointestinal fistulas treated at the University of California Medical Center, San Francisco from 1968 to 1977. There were 82 patients in the earlier group (1968–1971) and 104 patients in the later group (1972–1977). The groups differed in that 35% of patients in the earlier group received TPN, but 71% of patients in the later group received TPN. Of the patients who did not receive TPN, 93% had been adequately nourished using tube feeding methods. The two groups were otherwise similar. The fistula-related mortality (11%) and the spontaneous closure rate of the fistulas (32%) was unchanged over the ten year period. Thus, the principal impact of TPN was to simplify the nutritional management rather than to alter the outcome. When malignancy, previous abdominal irradiation, Crohn's disease, or a short (<2 cm) fistula tract were present, spontaneous closure was less likely than when none of these factors were present (20% versus 47%). Sixty-eight per cent of the deaths occurred in patients with uncontrolled sepsis. Fifty per cent of the deaths were due to the primary disease and were unrelated to the fistula. Spontaneous closure could not be expected to start until sepsis was controlled. Because over 90% of patients whose fistulas closed spontaneously did so within one month after infection was eradicated, we recommend operative closure for most fistulas that persist beyond that time. The most reliable operation is excision of the bowel from which the fistula arises with end-to-end anastomosis. Fistulas not amenable to excision should be managed by bypass.

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EXTERNAL GASTROINTESTINAL FISTULAS continue to cause significant morbidity and mortality even though many factors important to their management are known. Fourteen years ago, Chapman, Foran and Dunphy[3] emphasized the importance of adequate nutrition in the care of these patients and outlined a set of priorities for treatment. Fistula closure was more than twice as likely (89% versus 37%) in a group of patients that received over 1600 calories a day compared with those that did not. A follow-up report by Sheldon, Gardner, Way, and Dunphy[9] documented the success of this treatment regimen, noting that most patients could be given adequate nutrition by standard methods such as tube and enterostomy feelings. At the time of this last report, total parenteral nutrition (TPN) was a new technique, which had been used in only a few patients.

Several recent publications[1,5–8] have reviewed the treatment of gastrointestinal fistulas, and have assessed the impact of TPN on the results. Most authors concluded that TPN increased the rate of spontaneous closure of fistulas and decreased the mortality. Since the importance of nutrition has been a principal theme of our approach to therapy for many years, we felt that we were in a good position to assess the value of TPN in the management of patients with fistulas. Therefore, in this report we compared the results of treatment in recent years when most patients received TPN, with the results five to ten years ago when nutrition was usually provided by other means. Other principles of management have also been reassessed.

Clinical Material and Definition of Terms

We analyzed the records of all 186 patients with external gastrointestinal fistulas seen at the University of California Medical Center in San Francisco from 1968 to 1977. Only patients with fistulas proved by gastrointestinal x-rays, dye injection of the fistula tract, or laparotomy were included.

High output fistulas were defined as those that drained over 200 ml per 24 hours; low output fistulas drained less than that. Nutritional care of the patient was assessed by calculating the average daily caloric intake over the first, middle, and last weeks of treatment. Nutrition was considered to be "adequate" if 3000

Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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calories or more were supplied daily during at least two of these weeks. Patients were divided into those who received TPN and those who did not. All patients who received TPN had adequate caloric intake, but the majority of patients in the non-TPN group was also adequately nourished.

Fistulas that closed without direct surgical repair closed "spontaneously." Many such patients had other surgical procedures, usually drainage of a fistula-related abscess. "Septic" patients had fever (temperature >38.8°C) with or without purulent drainage from wounds, positive blood cultures, or they had an abscess drained during hospitalization.

Results

Over the ten year period, 186 patients were treated for enterocutaneous fistulas (Table 1). For purposes of analysis, they were divided into an early group (82 patients) treated from 1968 to 1972, and a later group (104 patients) treated from 1972 to 1977. The groups were similar in age and sex distribution, and in the proportion of high (46%) and low (54%) output fistulas. A higher percentage of patients was transferred to the University of California Medical Center in the later years (62% versus 49%), probably reflecting an awareness of our interest in this problem.

The mortality from all causes was similar in both groups (20%), but one-half of the 38 deaths were due to causes unrelated to the fistula (e.g., disseminated cancer). Table 2 shows the age distribution of the two groups, and the relationship of age to fistula-related mortality. In both groups the age distribution was similar; the mortality was higher (48%) in patients over 65 years. The fistula-related mortality for the entire ten year period was 11%, with no difference between the earlier (13%) and later (10%) years. The incidence of spontaneous closure of the fistula was higher in the later (35%) compared with the earlier period (26%), but the difference was not satistically significant (p = 0.11) (Table 3).

Tables 4A and 4B show the origin of the fistulas, their causes, and associated factors. The mortality in patients with gastric (31%), end-duodenal (20%), and jejunal (29%) fistulas was higher than the rest. The overall incidence of spontaneous closure of ileal or jejunal fistulas (22%) was lower than the rest. Spontaneous closure was also less likely when malignancy or Crohn's disease was present or when the distance between the fistula and the skin was short (<2 cm).

TABLE 2. *Age Distribution and Mortality*

Age (Yrs.)	1968–1971	1972–1977	All Patients		
			Total Patients	Fistula Related Deaths	All Deaths
<15	5 (7%)	13 (11%)	18 (10%)	0	3 (17%)
15–35	22 (31%)	14 (12%)	36 (19%)	4 (11%)	5 (14%)
36–50	16 (22%)	35 (31%)	51 (27%)	4 (8%)	11 (22%)
51–65	21 (29%)	35 (31%)	56 (30%)	7 (13%)	11 (22%)
>65	8 (11%)	17 (15%)	25 (13%)	6 (24%)	12 (48%)
Total	72	114	186	21 (11%)	41 (22%)

More patients had a nonoperative attempt at closure of the fistula in the later period (49% vs 35%) (Table 5). The proportion of patients in whom this approach was successful (73%), however, was unchanged throughout the study. About half of the patients in the recent group required operative closure of the fistula, a decrease of 10% from the earlier period. Operative repair of the fistula was successful in about 85% of cases in both groups.

Twenty-four per cent of patients in the earlier period received TPN, but in the later years the percentage increased to 71%. Nevertheless, of the 62 patients from 1968 to 1971 who did not receive TPN, 41 (66%) were adequately nourished by our criteria (Table 6). Nutrition was probably adequate in 18 of the remaining 21 patients, but the records were not detailed enough in these cases to calculate caloric intake. When those who were adequately nourished by tube feeding were compared with those who received TPN, neither mortality (7% versus 14%) nor spontaneous closure rate (22% versus 37%) of the fistulas was significantly different.

Seventy-two per cent of 91 patients who received TPN over the ten year period had no complications directly related to the TPN (Table 7). Catheter sepsis

TABLE 1. *Characteristics of Patients with Enterocutaneous Fistulas*

Characteristics	1968–1971 (72 Patients)	1972–1977 (114 Patients)	Total (186 Patients)
Male	36 (50%)	58 (51%)	94 (51%)
Female	36 (50%)	56 (49%)	92 (49%)
High output	54 (75%)	70 (61%)	124 (67%)
Low output	18 (25%)	44 (39%)	62 (33%)
Referred from other hospitals	35 (49%)	69 (61%)	104 (56%)
All deaths	16 (23%)	25 (22%)	41 (22%)

TABLE 3. *Mortality and Spontaneous Closure Rate**

	1968–1971 (72 Patients)	1972–1977 (114 Patients)	Total (186 Patients)
Fistula related deaths	9 (13%)	11 (10%)	20 (11%)
Other deaths	7 (10%)	14 (12%)	21 (11%)
Total deaths	16 (22%)	25 (22%)	41 (22%)
Spontaneous closure	19 (26%)	40 (35%)	59 (32%)

* There are no significant differences between the time periods.

TABLE 4A. *Relation of Origin and Cause of Fistula to Mortality and Spontaneous Closure Rate*

			All Patients		
Origin of Fistula	1968–1971	1972–1977	Total Patients	Fistula Related Deaths	Spontaneous Closure
Esophagus	6 (8%)	5 (4%)	11 (6%)	0	9 (82%)
Stomach	3 (4%)	11 (10%)	14 (8%)	4 (29%)	6 (43%)
Duodenum (end)	1 (1%)	7 (6%)	8 (4%)	2 (25%)	4 (50%)
Duodenum (side)	5 (7%)	6 (5%)	11 (6%)	0	3 (27%)
Jejunum	16 (22%)	32 (28%)	48 (26%)	13 (27%)	10 (21%)
Ileum	34 (47%)	38 (33%)	72 (39%)	7 (10%)	14 (19%)
Pancreas	3 (4%)	6 (5%)	9 (5%)	1 (11%)	6 (67%)
Bile Ducts	3 (3%)	8 (7%)	10 (5%)	2 (20%)	6 (60%)
Cecum/Appendix	4 (6%)	5 (4%)	9 (5%)	0	4 (44%)
Colon	13 (18%)	27 (24%)	40 (22%)	5 (13%)	12 (30%)
Rectum	3 (4%)	7 (6%)	10 (5%)	1 (10%)	3 (30%)
Cause					
Spontaneous	6 (8%)	6 (5%)	12 (6%)	5 (19%)	8 (30%)
Surgical Complications	66 (92%)	108 (95%)	174 (94%)	14 (10%)	52 (37%)

was suspected in nine patients (10%), and subclavian vein thrombosis occurred in six patients (7%). Suspected catheter sepsis occurred in 8% of patients in the later years, a frequency no different than that in other kinds of patients treated with TPN in our institution. There were deaths related to TPN therapy.

There were four patients with proximal high output fistulas (e.g., from the stomach or duodenum) who continued to lose 1500–2500 ml of secretions through the fistula per 24 hours even though they were receiving nothing by mouth and were on TPN. These patients were given cimetidine 300–600 mg IV q 6 hours and the fistula drainage promptly decreased to 300–800 ml per 24 hours. This greatly simplified maintaining fluid and electrolyte balance and the health of the skin around the fistula.

We analyzed in detail the factors that adversely affected outcome. Sixty-eight per cent of the deaths occurred in patients with uncontrolled sepsis; 73% of the deaths occurred in patients with small bowel fistulas; 78% of the deaths were in patients with Crohn's disease, cancer, or previous abdominal irradiation.

Sepsis

The incidence of sepsis (Table 8) at the beginning of treatment increased slightly in the two periods from 69% to 81%. The frequency with which sepsis was adequately controlled (by surgical drainage and antibiotic therapy) was similar (77%) in both periods. Control of sepsis was compared with the incidence of spontaneous closure and mortality (Table 9). When sepsis was controlled within one month, the spontaneous closure rate was 48%. When sepsis was never controlled, the spontaneous closure rate was only 6% and the mortality was 85%. Thus, failure to control sepsis was an ominous prognostic sign.

The duration of treatment once sepsis had been controlled was compared with the incidence of spontaneous closure (Table 10). Of the 43 patients whose fistulas closed without operation, 39 (91%) did so within one month after sepsis was controlled. The remainder (four patients) did so within an additional two months. All 16 patients who were treated beyond this time required operative closure of the fistula. Thus, spontaneous closure of a fistula was unlikely when non-operative therapy was continued for more than one month after control of sepsis.

Small Bowel Fistulas

There were 50 small bowel fistulas in the early period

TABLE 4B. *Other Factors Associated with Enterocutaneous Fistula*

			All Patients		
Factors	1968–1971	1972–1977	Total Patients	Fistula Related Deaths	Spontaneous Closure
Cancer	20 (28%)	23 (20%)	43 (23%)	4 (9%)	11 (26%)
Irradiation	7 (10%)	14 (12%)	21 (11%)	4 (19%)	3 (14%)
Crohn's Disease	8 (11%)	4 (4%)	12 (6%)	2 (17%)	1 (8%)
Short Tract to Skin (<2 cm)	7 (10%)	17 (15%)	24 (13%)	3 (13%)	4 (17%)

TABLE 5. *Outcome of Treatment*

	Nonoperative		Operative		
	Total	Successful	Total	Successful	Fistula-Related Deaths
1968–1971	25 (35%)	19 (76%)	47 (65%)	39 (83%)	9 (13%)
1972–1977	56 (49%)	40 (71%)	58 (51%)	49 (84%)	11 (10%)
Total	81 (44%)	59 (73%)	105 (56%)	88 (84%)	20 (11%)

and 70 in the later one. The mortality was the same in both periods (29%). The spontaneous closure rate increased slightly from 16% to 23%. Sixty-two per cent of small bowel fistulas were associated with one or more of the adverse factors discussed below, and in those with adverse factors the spontaneous closure rate was 18%. When no adverse factors were present, 27% of small bowel fistulas closed spontaneously.

Other Adverse Factors

The adverse factors (Table 11) with a major effect on outcome included Crohn's disease, cancer, abdominal irradiation, and a short fistula tract to the skin. Of 12 patients with Crohn's disease and a small bowel fistula, the mortality was 17% and only one fistula (8%) healed spontaneously. Mortality was highest (52%) in patients who had previously had abdominal irradiation for malignant disease. Fistulas with a short tract to the skin (<2 cm) were unlikely to close spontaneously (17%). When none of these factors was present, the mortality was 10%, and almost 50% of the fistulas closed spontaneously.

Results of Operative Repairs

Operative repairs (Table 12) included excision of the segment of bowel from which the fistula arose with end-to-end anastomosis, which was successful in 57 (86%) of the 66 patients in whom it was performed. Direct suture closure was successful in 19 (59%) of 32 patients. The fistula closed in all ten patients treated by bypass operations.

Discussion

The mortality associated with gastrointestinal fistulas has decreased since 1960 when Edmunds et al reported that 44% of their patients died.[4] Recent reviews report mortality rates from 6.5 to 21%.[1,8,9] While there have been many improvements in care, the use of TPN has been thought by some to be the major factor responsible for increased survival and improved results.

TABLE 6. *Effect of Nutritional Regimen on Mortality and Spontaneous Closure Rate in Patients with Adequate Caloric Intake*

Regimen	Number of Patients	Fistula Related Deaths	Spontaneous Closure
Tube Feeding, etc. (No TPN)	41	3 (7%)	9 (22%)
TPN	71	10 (14%)	26 (37%)

TABLE 7. *Complications of TPN*

Complication	1968–1971	1972–1977	All Patients
Pneumothorax	2 (10%)	1 (1%)	3 (3%)
Suspected Catheter Sepsis	3 (15%)	6 (8%)	9 (10%)
Subclavian Vein Thrombosis	1 (5%)	5 (7%)	6 (7%)
Hypertonic Dehydration	1 (5%)	3 (4%)	4 (4%)
Miscellaneous	1 (5%)	3 (4%)	4 (4%)
Total Complications	8 (40%)	18 (25%)	26 (28%)
Total Patients	20	71	91

Since the paper of Chapman et al in 1964,[3] the importance of adequate nutrition in the care of patients with enterocutaneous fistulas has been recognized. Nevertheless, malnutrition can develop quickly in the first few weeks after an anastomosis breaks down, and it is still common for patients to be malnourished when referred to a specialty center for care. Moreover, even if a patient does not have nutritional deficits, the increased caloric demands from sepsis, loss of protein-rich fluids and electrolytes, and the underlying disease require aggressive nutritional support to maintain the integrity of the immune system and the ability to heal wounds.

Nutritional needs can be met in several ways other than through TPN. Feeding of commercially available liquid diets by a tube passed beyond the fistula or through surgically created enterostomies has been used most widely.[2,10] In the early years of this study (1968–71), TPN was used in only 35% of cases, but over 90% of the remaining patients were adequately nourished with various tube feeding regimens. Occasionally, patients with low output and/or distal fistulas were adequately nourished with an oral diet, but in general, such patients have never been management problems. Of particular interest was the observation that the mortality of the group that was adequately nourished without TPN (7%) was no different than that of the group that received TPN during the later years (11%). These two groups were otherwise comparable (e.g., they contained a similar number of high and low output fistulas, etc.). Thus it appeared that TPN per se had

TABLE 8. *Incidence of Sepsis*

	1968–1971	1972–1977	All Patients
Sepsis on Admission	50 (69%)	92 (81%)	142 (76%)
Sepsis Not Controlled	11 (22%)	22 (24%)	33 (23%)

TABLE 9. *Effect of Sepsis on Mortality and Spontaneous Closure*

	Deaths	Spontaneous Closure
Sepsis Controlled Within One Month	5 (8%)	32 (48%)
Sepsis not Controlled	28 (85%)*	2 (6%)*

* $p < 0.003$

TABLE 10. *Relation of Duration of Non-operative Treatment after Control of Sepsis to Spontaneous Closure*

Duration of Treatment (Months)	# Patients Treated	Spontaneous Closure	Operative Closure
<1	70	39 (56%)	31 (44%)
1–3	23	4 (17%)	19 (83%)
>3	16	0 (0%)	16 (100%)
Total	109	43 (39%)	66 (60%)

no impact on fistula mortality, and that maintenance of adequate nutrition using more conventional methods was equally as effective.

We also examined the incidence of spontaneous closure of the fistula in these two groups. Although TPN increased the frequency of spontaneous closure from 22% to 37%, the difference was not statistically significant. Nevertheless, TPN has greatly simplified the nutritional management of patients with enterocutaneous fistulas, and we recommend its use as the primary means of providing nutrition in most patients. Full caloric and nitrogen replacement can be provided within two days of instituting TPN. Using tube feeding techniques, adequate caloric and nitrogen intake can only by achieved after 7–10 days because the osmotic load presented to the gut in the form of the liquid diet must be gradually increased to avoid diarrhea. Oftentimes it takes several days to pass a feeding tube past the fistula. The decreased fistula output which usually accompanies TPN greatly simplifies management, and the ability to avoid enterostomies for tube feeding decreases morbidity. Tube feeding still has a place in the management of some fistula patients, e.g., those with distal and low output fistulas, when fistulas are nearly healed, or when TPN is difficult or impossible to institute. Even though these patients often have abdominal abscesses and bacteremia, TPN appears to be safe, since the incidence of septic complications was no greater than usual.

Large fluid and electrolyte losses often persist in patients with a proximal intestinal (e.g., gastric, duodenal, proximal jejunal) fistula even when the patient is fasting and receiving TPN. The effectiveness of cimetidine in decreasing fistula output in a few such cases was striking, and greatly simplified both fluid and electrolyte management and control of the fistula.

Uncontrolled sepsis is an ominous sign which in our experience was associated with a 85% mortality. Because the majority (81%) of patients are septic at the time of admission to the hospital, surgical drainage of abscesses within the first 48 hours is a critical part of patient management. We have previously outlined the priorities for management of these patients, stressing this point and the fact that a continuing search for new abscesses is required during treatment.[9]

Definitive surgical treatment of the fistula should not be combined with drainage of the abscess. Although such an approach is occasionally successful,[1] more frequently it is not, and may result in a recurrence of the fistula and spreading of the infection to previously uninvolved areas in the abdomen. Moreover, when sepsis was controlled within one month of admission to the hospital, about half of the fistulas closed spontaneously.

It has been difficult in the past to decide when conservative therapy should be discontinued in favor of operative closure of the fistula. Some patients have been treated for many months in the vain hope that the fistula might close spontaneously. In our experience spontaneous closure could not be expected to start until sepsis was controlled. But after infection was eradicated, over 90% of patients whose fistulas were going to close spontaneously did so within the next month. Less than 10% of fistulas closed in the two months thereafter (i.e., in the second and third months after control of sepsis), and none closed spontaneously

TABLE 11. *Influence of Adverse Factors on Mortality and Spontaneous Closure*

	Crohn's Disease	Cancer	Abdominal Irradiation	Short Tract (<2 cm)	All Patients	No Adverse Factors
Deaths	2 (17%)	12 (28%)	11 (52%)	7 (29%)	41 (22%)	9 (10%)
Spontaneous Closure	1 (8%)*	1 (26%)	3 (14%)	4 (17%)	59 (32%)	40 (47%)
Total	12	43	21	24	186	86

* $p < 0.05$ relative to all patients.

TABLE 12. *Results of Operative Repairs*

	Kind of Operation		
	Direct Closure (32 Patients)	Excision (66 Patients)	Bypass (10 Patients)
Fistula Closed	19 (59%)	57 (86%)	10 (100%)
Total Deaths	11 (34%)	11 (17%)	0
Fistula-Related Deaths	5 (16%)	7 (11%)	0

after three months of non-surgical therapy. Therefore, if a fistula has not closed spontaneously within the first month or so after sepsis is controlled, operative closure may be scheduled, since there is relatively little hope (<10%) that surgery would not be required eventually. Except for an occasional low volume distal fistula, there seems to be almost no reason to delay operative closure of persistent fistulas beyond three months after control of sepsis. Of course, if at the end of a month of observation the fistula drainage is decreasing and the patient's condition is improving, operation to repair the fistula may be delayed longer.

There are situations in which spontaneous closure of the fistula is especially unlikely. We operated early on several patients where there was obstruction distal to the fistula and lack of gastrointestinal continuity. Other factors that made spontaneous closure less likely were Crohn's disease, malignancy, abdominal irradiation, and a short tract to the skin. When a small bowel fistula was associated with Crohn's disease, the incidence of spontaneous closure was only 8%. The spontaneous closure rate for small bowel fistulas associated with abdominal irradiation was only 14%. When the length of the fistula tract to the skin was less than 2 cm, the incidence of spontaneous closure was 17%. The low closure rate in irradiated bowel or bowel involved with Crohn's disease is probably due to the general poor healing of these tissues. The low rate of spontaneous closure in patients with short fistula tracts is most likely due to epithelialization of the fistula tract down to the opening into the bowel. The spontaneous closure rate of small bowel fistulas in the absence of any of these factors was 32%. Therefore when any of these factors is present, one might consider earlier attempts at operative closure.

Several factors were associated with the inability to control sepsis in 32 patients. One-third of this group had malignant disease and one-quarter had irradiated bowel. This suggests that the seriousness of the associated disease with its possible effect on immunologic competence, and the impaired blood supply of irradiated tissue contributed to the poor result. Eighteen patients (56%) who died with uncontrolled sepsis were never operated upon, because it was impossible to determine from physical examination or other tests where the infection was located. At autopsy, six (33%) of these patients had focal undrained abdominal abscesses. Surgery was not indicated in these patients owing to the presence of incurable malignant tumor, acute cardiac complications, etc. In general, however, abdominal exploration to find and drain an abdominal abscess should be performed in septic patients who are losing ground even if diagnostic studies have not pinpointed an abscess.

Operative Management

When the decision for operation is made, the patient should be in optimal nutritional shape. Protection of the skin near the fistula opening should allow for an incision through healthy, uninflamed tissue that can be expected to heal without infection.

In general, the best operation is excision of the segment of bowel from which the fistula arises and end-to-end anastomosis. This approach was successful in 89% of our patients. Bypass of the fistula may be preferable, however, in situations where excision would entail a more complex and hazardous procedure. This is often the case for lateral duodenal fistulas or small bowel fistulas that arise deep within the pelvis. In our experience, bypass in 10 patients was uniformly successful, but because the diseased segment is left behind, we only recommend it for special cases. Direct suture closure of the fistula cannot be recommended because the closure often breaks down; it failed in 41% of the 32 patients in this series in whom it was tried. There is often a temptation to use direct suture closure in the same kind of situation that might be managed better by bypass—when excision and re-anastomosis would be difficult. Bypass is preferred under these circumstances because the fistula itself can be left undisturbed, a hazardous dissection can be avoided, and failure is manifested only by persistence of the fistula instead of diffuse peritoneal contamination.

Acknowledgment

We acknowledge the expert secretarial assistance of Dorothy Archbold, Judith Barbee, Charles Case, and Cynthia Nelson.

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DISCUSSION

DR. LLOYD D. MACLEAN (Montreal, Quebec): I greatly enjoyed this paper. Our own results may seem different at first glance.

(Slide) We also looked at a recent ten-year interval at the results we were achieving. These are all high-output small bowel fistulas. We excluded the duodenal stump cases, because they could be treated by drainage and intubation, and we excluded carcinomatosis patients, whom one wouldn't aggressively treat.

Prior to nutrition, and in the group of 66 on the left there, the mean caloric intake was only 500 per day. These patients were not all that amenable to tube feeding.

The nonoperative cure rate was 27%, surgical care, 32%, and this was done at various intervals, and it seemed to make no difference; that is, those who were operated early didn't get any better results than those who were operated upon a month later or, in fact, those who were not operated upon at all. A third of those patients died.

In marked contrast, after we started using total parenteral nutrition in 25 patients on the right, treated, later in the series, the results improved. They received 2500 calories a day, mean, and the nonoperative cure rate was 56%, surgical cure, 36%, and only two of those patients died, one after eight months.

I have a couple of questions. What was the caloric intake in your patients, both before and after TPN in this series, as a guide to us?

I think we've all read earlier papers of Dr. Dunphy. It was my impression that he had treated some patients intravenously with somewhat less than we are accustomed to use with total parenteral nutrition but the amount is probably adequate. This was in the area of 1500 to 1800 calories a day, that could be achieved with Amigen and 5% glucose without T.P.N.

I wondered if you do have advice on caloric and protein requirements, especially in the septic, high-risk group. We have found it very difficult to cure sepsis by any means, whether surgical or with other means, in the nutritionally depleted patient.

DR. THOMAS F. NEALON, JR. (New York, New York): Although I certainly want to agree with everything Dr. Dunphy said, I don't think that the point about the impact of TPN on the management of their patients would pertain in terms of the patients that we have been taking care of, and as I looked at it and listened to this, I think there probably are two different areas. One is the type of patients.

First of all, we see many patients with trauma. We see a fair number of patients who are in inordinately poor condition before they're operated on. They have neglected themselves for years, and then, when they have a major catastrophe on top of that, they create further problems.

I also think we have to face the fact that we were not doing a good job of nourishing our patients properly until we did get TPN available; this has probably been a major fact, in that since the availability of this technique, we have had more time to get these patients ready. We've been allowed to make more mistakes, and we have had to do fewer definitive operations on them.

This is going to be a routine protocol for my house staff in taking care of these patients in the future.

DR. JAMES DUKE (Houston, Texas): I would like to agree with the point that was just made about the peculiarity of various patient groups, which many of the members and guests have had the opportunity to care for.

I have just had occasion to review my experience at the University of Texas Medical at Houston. As you probably know, we've been there six years, and I believe that you can imagine, while you're trying to establish yourself in a new community, you're not going to get the best referral pattern that might occur. In that period of time, I have personally taken care of 40 patients with fistulas. The mortality rate in this group was 15%.

Nine of these patients with fistulas had a malignancy, and we had a 73% mortality in that group. If you take them out, then you get over into another peculiarly intradepartmental difference in that Dr. Dudrick, as you might suspect, has a very good referral practice with inflammatory bowel disease. I happen to get a complication of, basically, obstructive disease that doctors have had trouble with.

Now, in that group of 31 patients we had a mortality rate of 7%. One of these was a Jehovah's Witness who would not receive blood. The other had massive sepsis and hardly fits into the group.

There are one or two comments I would like to make, based on my experience with these. Four of these patients have been treated for between 150 and 300 days, trying to get closure and dealing with all the other problems. The thing that has impressed me the most that is an extension of this very fine paper, in my effort to try, and try not, to operate on these people, is that if you wait—I appreciate the data of one month being an ideal time at which there is a drop, and spontaneous closure does not occur—but if you do, in fact, wait two or maybe three months, the patient has sufficiently resolved the process, assuming adequate drainage has been accomplished, such that the procedure is not all that difficult.

On several occasions, I have had the referring physician watching over my shoulder as we did this, and almost uniformly they say, "My, it wasn't like that when I was in there!" I think it's a worthy point to at least consider.

In the group of people that had postoperative complications that are not malignant, we had a spontaneous closure rate of 42%, right in the realm of where we're talking about here.

DR. JOSEF E. FISCHER (Boston, Massachusetts): There is a great wealth of information in this presentation of a large number of patients. I believe this is one area where review of a large number of patients can really give us perspective on what to do in the future.

Dr. Soetens and I have had the opportunity to go through 420 cases of fistulas at the Massachusetts General Hospital since 1945. This society was privileged to hear what I think was a classical presentation by Dr. Welch's review of 160 patients in 1960, in a paper by Edmunds, Williams and Welch.

It is interesting that in our hospital the mortality dropped not between 1960 and 1970, but between 1960 and the early 1960's, from an average mortality of about 42% to 15%.

Now, part of this is undoubtedly the influence of nutrition. Dr. Welch's paper made the point that no patient with malnutrition survived a high-output fistula in 1960; and since that time, various jerry-rigged means of getting nutrition into patients were used. Still the advent of hyperalimentation does not seem to have dramatically affected mortality in our particular institution.

On the other hand, there are two points that I would like to make here. First, as far as the time of spontaneous closure, there is a significant number of patients who do close at about six weeks, and these are mostly the patients with ileal fistulas. Second, while mortality has not dropped in this period, spontaneous closure has increased from about 10% to 35%. I have a feeling that we probably lose patients whom we might have saved had we waited a little longer before operating.

My question refers to one problem which is inherent in all papers of this nature, and that is case selection. In the data from 1968 to 1971, it seems that there were only 60% of the patients in the group who were nourished with tube feedings, and they had a mortality of 7%. My question is: What happened to the other 40% of patients?

My guess would be that those would be patients with peritonitis, a lot of abscesses, whom you could not tube feed. I would be willing to bet that the mortality in that group might have been considerably higher without hyperalimentation. This group of patients who can't tolerate tube feedings, I think, is the group that really benefits from hyperalimentation. It is in this particular subgroup of patients with fistulas that the contribution really is immense and saves a lot of those patients.

Dr. J. Englebert Dunphy (Closing discussion): We have regarded 3000 calories, provided one way or another, as adequate nutrition. Some patients received more than that; very few received less. In the early period, before we had total parenteral nutrition, we went to the most extraordinary lengths to provide calories. Some patients did receive some calories by vein, but the majority were fed through various fistulous tracts, by collecting material, mixing it with solutions and preparations and then putting it either above or into a feeding jejunostomy.

Now, the complications were somewhat greater. Patients had problems of additional wounds. There's no question that TPN has enormously simplified the care of these patients.

With regard to the source of the patients, both the Oregon series and the California series, the vast majority were referred to us from other hospitals. Often, surgeons just don't want to believe they have a problem, and the majority of patients, particularly in the earlier years in both series, came to us profoundly septic and cachectic, and an operation under any circumstances on those patients would have been fatal.

As to the discussion of when to operate, I think that we're not talking about delay from the time of admission; we're talking about a one month's delay after you have completely controlled infection, if it's controllable, and after nutrition is thoroughly adequate, and the patient is gaining weight. At that point, in most patients, you can tell within a week that things are beginning to look up. The fistula isn't putting out quite so much, and over the next few weeks it's quite obvious that it is going to close spontaneously.

Now, if it improves a little, then the drainage increases again, and after a month, you can be certain that the fistula is not going to close. There are many specific factors, so it is very important to define the fistula. There are a lot of points we haven't gone into here, in addition to defining the nature of the fistula by barium studies and fistulograms. This should be done fairly early, as it is an extremely important point in management. We haven't touched upon the whole question of caring for the skin, but this is also a critical factor in improving the over all care.

In reply to Dr. Fischer, the patients not claimed to be adequately nourished by tube feeding had no more severe disease nor did their outcome differ compared with th rest of the group. We think that most of them were adequately nourished by tube feeding, but their records were incomplete.

I would say that most of our patients now receive total parenteral nutrition, but there are patients that don't need it. When refeeding is simple it may be better to avoid the complications of TPN, even though these can be kept to a minimum. It's unnecessary to put every patient on parenteral feeding, when it's easy to collect the losses and reintroduce them, or, in some instances, to just feed the patient. With fistulas low in the ilium, losses may be high, but one can provide nourishment simply without TPN medication.

One point about the patients whose sepsis was not controlled: the majority of those had generalized sepsis. I'd like to stress the point that if there is any question about residual abdominal sepsis, even though there are no localizing signs, it's essential to reoperate and look for abscesses. Never let a patient go downhill simply because you can't pinpoint or localize the site of the sepsis within the abdomen by physical exam or x-ray.

Most of the patients that died from infection were the patients with cancer and other complicating diseases, or generalized sepsis, particularly pulmonary sepsis.

Failure of Low Dose Heparin to Prevent Pulmonary Embolism After Hip Surgery Or Above The Knee Amputation

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In a randomized, double-blind trial, 5,000 USP units of sodium heparin or saline were given subcutaneously at least two hours before surgery and at 12 hour intervals thereafter to patients requiring total hip replacement, surgical correction of hip fracture, or major lower extremity amputation for vascular insufficiency. Lung perfusion scans were performed before surgery and at weekly intervals during the postoperative period. Pulmonary arteriograms were requested in patients developing new perfusion defects on serial scans. Two hundred twelve patient hospitalizations were analyzed. We diagnosed acute pulmonary embolism by serial lung perfusion scans or at autopsy in 37 patients. The incidence of pulmonary embolism in 40 patients with below the knee amputation was too low to warrant conclusions. The incidence of acute pulmonary embolism in 94 patients undergoing above the knee amputation was 25% in patients receiving heparin and 27% in patients receiving saline. The incidence of acute pulmonary embolism in 78 patients undergoing hip surgery was 13% in patients receiving heparin and 12% in patients receiving saline. We conclude that the regimen used had no significant effect on the incidence of acute pulmonary embolism in patients undergoing hip surgery or above the knee amputation.

ACUTE PULMONARY EMBOLISM from venous thrombi is an important cause of death in bedridden patients. Studies have shown that sodium or calcium heparin in divided doses totalling 10,000 to 15,000 international units (IU) or USP units per day can reduce the incidence of venous thrombosis in some populations of medical and surgical patients.[2,6,7,13,14,22,25,26] Controlled studies of postoperative pulmonary embolism have shown that low doses of heparin can reduce the incidence of pulmonary embolism after major thoracic or abdominal surgery,[12,16,20] although one group reported no reduction in pulmonary embolism despite reduction in venous thrombosis.[8] Effective regimens tested caused few complications and were thought not to require laboratory monitoring, although excessive wound hematomata had been reported after 5,000 USP units of sodium heparin three times daily.[11]

Despite these investigations, the efficacy of low dose heparin remains uncertain in other groups of patients at particularly high risk of pulmonary embolism. In patients requiring hip surgery, 5,000 IU sodium or calcium heparin three times daily reduced venous thrombosis in some representative prospective studies.[18,21] Smaller doses of sodium heparin in hip surgery patients appeared to reduce fatal pulmonary embolism in a non-randomized study;[23] other studies failed to show reduction of venous thrombosis.[5,9] Somewhat different treatment regimens were used in each of these studies.

Patients undergoing major amputation of a lower extremity for complications of ischemic disease are also at high risk for pulmonary embolism,[27] but have not been thoroughly studied.

We have prospectively investigated the effect on pulmonary embolism of 5,000 USP units of sodium heparin given twice daily to patients undergoing hip surgery or major amputation of a lower extremity.

Patients

Patients requiring hip surgery because of hip fracture, total hip replacement for joint disease, or major lower extremity amputation for the complications of ischemic vascular disease were studied after obtaining their informed consent. No other selective criteria

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

Supported in part by grant RO1 GM22890 from the National Institutes of Health and Medical Research Service of Veterans Administration.

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0003-4932/78/1000/0468 $00.85 © J. B. Lippincott Company

were applied. Patients were assigned in a blind manner, using a random number table, to receive either saline or a solution containing 10,000 USP u/ml of beef lung sodium heparin. Patients received 0.5 ml of the coded solution subcutaneously every 12 hours for two weeks or until discharge. Administration of the drug was begun as soon as possible after admission of patients with hip fracture, and about two hours before operation in patients requiring amputation or elective total hip replacement.

Whenever acute pulmonary embolism was detected, the patient was withdrawn from the study and managed by his physician.

All patients were cared for by the surgical services of the College of Medicine of the University of South Florida at the Tampa VA Hospital or at the Tampa General Hospital, between January 1974 and July 1977.

Materials and Methods

Lung Studies

A lung perfusion scan was performed before operation and then at weekly intervals for as long as the patient received the drug. After slow intravenous injection of 2-3 mCi of ^{99m}Tc labeled albumin microspheres (3M Company, Minneapolis, Minnesota), images of at least four projections were obtained with a rectilinear scanner or gamma camera.

Pulmonary arteriography was requested in each patient developing a new pulmonary perfusion defect which was recognized on serial lung scans by physicians of the nuclear medicine services. A No. 6 French "pigtail" catheter was introduced into the pulmonary artery under fluoroscopic guidance, with electrocardiographic monitoring. Forty milliliters of 76% diatrizoate meglumine or diatrizoate sodium was injected over two seconds into the right or left main pulmonary artery, and serial roentgenograms were obtained for 12 seconds after each injection. The anteroposterior projection was used for imaging the right lung; a 30 degree right posterior oblique projection was used for imaging the left lung. Additional selective angiograms were performed in doubtful cases. Plain chest roentgenograms were used for assistance in interpretation of arteriograms and perfusion lung scans.

Lung Scan Analysis

At intervals of six to 12 weeks, J.W. and E.E. reviewed lung scans without knowledge of arteriographic results, patient symptomatology, or treatment received. Lung scan series were classified as follows:

1) If, after the initial scan, a new lobar, segmental, or subsegmental perfusion defect appeared which was not attributable to an infiltrate, pleural effusion, vascular congestion, or atelectasis appearing on the chest roentgenogram, the study was categorized as "high probability" of acute pulmonary embolism.

2) If no new perfusion defect appeared in serial scans, the study was categorized as "no" acute pulmonary embolism.

Series showing other perfusion changes were not considered, for data analysis purposes, to show acute pulmonary embolism. These studies were categorized as:

3) If a new perfusion defect appeared that was possibly lobar, segmental, or subsegmental, both without associated roentgenographic findings, the study was categorized as "moderate probability" of acute pulmonary embolism.

4) If a new perfusion defect appeared that clearly crossed segmental boundaries or was clearly attributable to changes in heart size, or overall pulmonary blood flow distribution, or was attributable to other disease by roentgenograhic evidence, the study was categorized as "resolving pulmonary perfusion defect." embolism.

An additional category was established for a few patients:

5) If a lobar, segmental, or subsegmental perfusion defect not attributable to chest roentgenographic abnormalities was present on the initial lung scan, and showed resolution on subsequent scans, the study was categorized as "resolving pulmonary perfusion defect".

Patients with unchanging nonsegmental or diffuse patchy perfusion defects were classified as having chronic pulmonary disease in addition to any classification based on changes in perfusion distribution.

Pulmonary Arteriogram Analysis

All pulmonary arteriograms were reviewed by S.G., J.W., and E.E. without knowledge of the treatment received. Pulmonary embolism was diagnosed if the patient showed an intraluminal defect or abrupt vessel cutoff. Indirect signs such as localized slowing of blood flow, oligemia, or a reduction in the number of vessels were not considered specifically diagnostic for acute pulmonary embolism.

Autopsies

At autopsy, the pulmonary arterial vessels were examined for thrombi to the third division by a pathologist who did not know what drug treatment had been given to the patient. Any thrombi discovered were recorded and their age was estimated by gross and microscopic examination.

Results

Between January 1974 and July 1977, 283 patients entered the study. After deletion of patients because of inadequate compliance with the protocol, 212 study patients remained for analysis; seven patients were studied during two separate hospitalizations.

Thirty patients were female. The mean age was 64.5 years, with a range of 23–87 years. Chronic pulmonary disease detected as unchanging perfusion abnormalities on lung perfusion scanning was diagnosed in 187 patients. Table 1 shows the incidence of complicating diseases in the study patients.

Serial lung scans were reviewed and categorized according to the estimated likelihood of acute pulmonary embolism, or other categorization as shown in Table 2. Pulmonary arteriograms were reviewed in 20 patients who had lung scan series categorized as high probability of acute pulmonary embolism. Emboli were detectable in 18 (90%).

As an index of the incidence of acute pulmonary embolism in the study population, we diagnosed acute pulmonary embolism only in patients who had lung scan series in the high probability category, or who had acute pulmonary embolism detected at autopsy. There were not enough patients in other lung scan series categories to warrant additional analyses. A total of 37 patients were diagnosed in this manner as having acute pulmonary embolism.

Statistical Analysis

After all patients were categorized, the drug code was broken. Table 3 shows that heparin treatment had no significant effect on the incidence of acute pulmonary embolism in any of the groups. The analyses of the data for the hip surgery and the above the knee amputation groups were based on the normal approximation to the binomial distribution, but Fisher's exact test for a 2 × 2 contingency table was used to analyze the small sample data of the below the knee amputation group.[3] In addition to testing for significant differences between the groups, we estimated the probability that we would have failed to detect reduction in pulmonary embolism comparable to the 87% reduction reported in the largest autopsy series.[12] This probability is less than 0.03 for patients with above the knee amputation, 0.35 for patients with hip surgery, and ~1.0 for patients with below the knee amputation.

TABLE 1. *Characteristics of Study Patients: Complicating Diseases*

	Surgery Performed			
	Above Knee Amputation	Below Knee Amputation	Hip Surgery	Total
# Patients	94	40	78	212
# Patients With:				
Carcinoma	5	2	2	9
Diabetes Mellitus	25	8	6	39
Congestive Heart Failure	12	5	8	25
Cerebrovascular Accident	18	5	4	27
Venous Disease	4	4	3	11
Resolving Pulmonary Perfusion Defect	9	0	6	15

TABLE 2. *Pulmonary Embolism Diagnosed by Serial Lung Scans or Autopsy*

	Surgery Performed		
# Patients	Above Knee Amputation	Below Knee Amputation	Hip Surgery
Embolism at Autopsy	3	0	0
Lung Scan Probability Category:			
High	22	2	10
Moderate	3	1	0
Low	6	0	4

Ten patients died during the study, too few for an assessment of the effects of treatment on lethal pulmonary embolism or on overall mortality. Of the five patients undergoing autopsy, three above the knee amputees had recent acute pulmonary embolism. All three patients were receiving saline.

The incidence of postoperative bleeding severe enough to be recorded as unusual by the attending surgeons was similar, and less than 10%, in the heparin and saline treated groups. One patient who received saline was removed from the study prematurely because of excessive bleeding.

Discussion

Our results show that the heparin regimen we tested did not help patients with the highest incidence of acute pulmonary embolism: those undergoing hip surgery or above the knee amputation. We studied too few patients to warrant conclusions about the effect of treatment in patients undergoing below the knee amputation.

In designing this study, we recognized limitations in the methods commonly used in diagnosing pulmonary embolism. Pulmonary embolism diagnoses based on clinical data only or on a single postoperative lung scan are open to question. An isolated lung perfusion scan is a highly sensitive way to detect pulmonary embolism, but perfusion defects on isolated examinations are frequently nonspecific.[19,24] In some populations, radioxenon lung ventilation scans may help in interpretation of lung perfusion scans,[17] but we found this study to be less helpful in our population because of the high prevalence of ventilation abnormalities due to chronic lung disease. Pulmonary arteriography is a more specific method for diagnosing pulmonary embolism, but we considered this invasive procedure impractical for serial use. Isolated lung perfusion scans or isolated arteriograms may fail to distinguish recent and old emboli. It was impossible for us to study enough patients to base conclusions on autopsy results alone.

The index we used of the incidence of acute pulmonary embolism is unbiased and minimizes these limitations. We used autopsy findings when available. In addition, we compared preoperative and serial postoperative lung perfusion scans, and requested arteriography in patients in whom new perfusion defects were recognized. At a later date we categorized patients for the likelihood of acute pulmonary embolism, based upon independent judgement of the characteristics of perfusion distribution in serial scans. We obtained pulmonary arteriography in about 60% of patients that were placed in the category of high probability of acute pulmonary embolism on the basis of lung scans. Ninety percent of these patients had arteriographic evidence of embolism. We concluded that serial lung perfusion scans provide an unbiased and relatively specific index of acute pulmonary embolism.

We suspected that the rate of acute pulmonary embolism could more accurately predict the rate of fatal pulmonary embolism than would the rate of venous thrombosis. Other investigators have confirmed that the effect of treatments on the incidence of pulmonary embolism may differ from the effect on venous thrombosis.[4,8,15,16] Measurements of I-125 fibrinogen uptake as an index of deep venous thrombosis would be a particularly difficult test of heparin effect in patients with leg amputations. Tissue damage would most likely cause many equivocal studies, and venography for confirmation would not often be feasible.

Our finding that the incidence of pulmonary embolism was four times higher in patients undergoing above the knee amputation than below the knee amputation is probably attributable to reduced mobility and greater tissue necrosis in the former group of patients.

Our study population differed in important ways from populations undergoing major abdominal and thoracic surgery in which low dose heparin has been found effective in reducing pulmonary embolism.[12,16,20] Patients with hip surgery, total hip replacement, and ischemic disease of the lower extremity often have more extensive tissue necrosis than patients undergoing other types of surgery. This may act as a stimulus to fibrin formation and clotting, so that in many patients the capacity of low doses of heparin to prevent venous thrombosis is exceeded.

If an excessive clotting stimulus in high risk patients accounts for the failure of our heparin dose, a different regimen might more nearly counteract the stimulus. However, increased bleeding found after administration of 5,000 USP units of sodium heparin three times daily[10,11] shows the need for discretion in increasing prophylactic heparin doses above those we used.

The low dose heparin regimen that we tested was not the same as that used by any of the European investigators who have reported on the incidence of acute pulmonary embolism.[1] The 5,000 USP units of sodium heparin that we used twice daily may have a somewhat greater anticoagulant effect on the 5,000 IU sodium heparin administered twice daily in some studies, and differ in effect from the 5,000 IU calcium heparin administered three times daily on others.

Until the predictive value of embolism detected by serial lung pefusion studies for fatal pulmonary embolism is established, we would not consider such studies to be a substitute for autopsy studies. It is possible that the regimen that we tested might reduce fatal pulmonary embolism even though it did not appreciably affect the overall rate of embolism, or that a regimen that reduced minor embolization detected on lung scans might fail to reduce fatal embolism.

Formidable logistic problems make it impractical to test all proposed treatments by autopsy or mortality studies. We suggest that studies equivalent to ours are a plausible means of screening treatments before initiating autopsy based studies of treatments in patients at high risk of acute pulmonary embolism.

TABLE 3. *Treatment Results*

	Heparin		Saline		
Surgery Performed	# Patients	# Pulmonary Embolism	# Patients	# Pulmonary Embolism	probability
Above Knee Amputation	53	13 (25%)	41	12 (29%)	0.39
Below Knee Amputation	16	1 (6%)	24	1 (4%)	0.85
Hip Surgery	37	5 (14%)	41	5 (12%)	0.70

Acknowledgments

We acknowledge the technical assistance of Ms. Sandra Perschall and Mr. I. Przekop, and the assistance of Dr. Stephen VanVoorst and Dr. Robert Routon.

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DISCUSSION

DR. EDWIN W. SALZMAN (Boston, Massachusetts): I think this interesting and important study will be a major contribution to the literature. The authors' conclusions seem fundamentally sound and conservative, although there is an element of uncertainty. Only half of the patients with a diagnosis of pulmonary embolism had the diagnosis confirmed by angiography, the diagnosis was by perfusion scan without ventilation scan and the three patients who had pulmonary embolism at autopsy were all in the control group, and there were none in the heparin group. So I should like to ask the authors about the distribution of autopsies and deaths and angiography between the control and the heparin group.

Nonetheless, I think the conclusion is fundamentally correct: that is, that low-dose heparin is really not adequate protection in patients at very high risk of venous thromboembolism.

Two major questions follow this conclusion: is minidose heparin effective in other patient groups, and what form of prophylaxis is appropriate for patients at high risk?

In regard to othopedic cases, particularly reconstructions of the hip, there have been twelve prospective controlled trials in patients undergoing hip surgery that have used objective diagnostic methods, such as labeled fibrinogen scanning. Eight of the trials have had a positive result, but the effect was often marginal. Over all, using this diagnostic method, 50% of the patients in control groups have had venous thrombosis, versus 19% with low-dose heparin.

However, there have been only two trials in which patients were studied by venography, which is important in this patient population because of the high rate of proximal thrombi not detected by fibrinogen scanning. Both of these trials were negative. There have been no previous reports before the present study on protection against pulmonary embolism after hip operations.

In general surgery the situation is quite different, however. There have been twenty-one prospective controlled trials for venous thrombosis using objective diagnostic end points in patients undergoing abdominal and thoracic operations, a group which includes almost 7000 patients. All but three of these 21 trials have found significant protection by low-dose heparin against venous thrombosis. The three negative trials were small and involved a total of less than 400 patients.

The collected results of these 21 trials in the aggregate show a rate of DVT of 7% with low-dose heparin, against 26% in the control group. This difference is highly significant.

In regard to pulmonary embolism in general surgical patients, there have been five prospective trials using objective diagnostic techniques. Four of the five showed protection with low-dose heparin. The one negative study had only about 100 patients in it, in contrast to the multicenter trial, conducted by Kabbar and associates involving over 4000 patients. They found a significant reduction in both fatal pulmonary embolism and total pulmonary embolism at autopsy.

There has been some criticism directed at details of this study, but the conclusion appears fundamentally sound, and it does seem to prove that low-dose heparin can protect patients at moderate risk against both venous thrombosis and pulmonary embolism.

The second major question is, "What is appropriate for prophylaxis in very high-risk patients, or, to put it more broadly, what should be one's posture with regard to treatment of patients in various clinical settings?"

The problem is selection of the best method for a specific patient from the several effective agents now available. There are gaps in the data, particularly with regard to protection against pulmonary embolism, because in most patient populations the frequency of pulmonary embolism is so low that it takes a very large study to give clear-cut results. In the absence of evidence to the contrary, it seems reasonable to extrapolate from protection against venous thrombosis as our best approach to the prevention of pulmonary embolism. Based on this view, we suggest the following approach to patients at risk.

In the very high-risk patient, the most effective agent is probably warfarin, which can be given in therapeutic dosage even for prophylaxis. Bleeding complications are increased by warfarin and it probably should be reserved for very high-risk cases. General surgical patients under the age of forty we believe, do not require prophylaxis, unless they have some special predisposing cause such as a prior history of venous thromboembolism. Over age forty the rate of this complication increases, and here low-dose heparin and external pneumatic compression of the calves with inflatable boots seem about equally effective. Data are somewhat limited with external pneumatic compression, especially in regard to pulmonary embolism.

In orthopedic cases, warfarin, aspirin and dextran seem to be effective. Low-dose heparin, as today's authors have reported, is not the preferred agent in this group.

The take-home message, I believe, is that there are a number of agents available for protection, and our task is to select the method of prophylaxis most appropriate in different clinical settings.

Dr. F. William Blaisdell (San Francisco, California): I have very little to contribute which would be an addition to those comments made by Dr. Salzman, except to say that this study aims for the mark, which is to point toward the prevention of pulmonary embolism rather than of leg vein thrombosis.

I, for one, have trouble with all the efforts directed toward preventing lower leg thrombosis—particularly by mechanical means—when it is evident that most fatal pulmonary emboli come from large veins in the upper thigh and in the pelvis. In addition, the sequelae of the lower leg vein thrombosis appear to be minimal, since disability from asymptomatic leg vein thrombosis occuring so commonly in surgical patients is apparently minimal.

The five studies that Dr. Salzman mentioned are actually the only ones directed toward the prevention of pulmonary embolism. The problem, of course, is that low-dose heparin may be effective under some circumstances but not under others. The dilemma is that in those circumstances such as above-knee amputation, where it's needed the most, it may not be effective.

One of the questions I would like to ask the authors is whether or not, on the basis of their documentation that above-knee amputation has a 25% incidence of pulmonary embolism, they would advocate some more potent form of therapy such as the administration of larger doses of heparin or of Coumadin.

I would like to add that, although Kakkar's multicenter trial of low-dose heparin appeared to be definitive, several of the centers included in the study have challenged some of the data. As a result, further studies like this one should continue. This is a commendable effort to document the effect of low-dose heparin therapy. I very much enjoyed the opportunity to read the manuscript, and I commend the authors on their presentation.

Professor Lars-Erik Gelin (Goteborg, Sweden): I agree with the authors that postoperative and posttraumatic thromboembolism remain a major problem in surgery, because, even if prophylactic measures have proven to decrease the incidence of venous thrombosis by about 50%, either the prophylaxis is anticoagulation with dicumarol or heparin, dextran or leg elevation with intermittent pulsation pressure, thromboembolism still is a major threat to successful surgical care.

We have been interested in thromboembolism in our institution for a long time, and have tried, both experimentally and clinically, to evaluate different prophylactic measures in high risk groups.

(Slide) In a series of 94 patients with fractures of the femoral neck, 39 received heparin and 55 received dextran 70 as prophylaxis. The incidence of venous thrombosis was the same in both groups, as detected with labeled fibrinogen method.

(Slide) In a prospective double-blind study of the prophylactic effect of preoperative hemodilution, with either glucose as a control and dextran 70 or dextran 40, when given as an infusion at the initiation of anesthesia only, to 901 consecutive patients above the age of 50 and undergoing major abdominal surgery, at break of the code we found the following incidence of thromboembolic complications. As you see, the incidence of thromboembolism decreased at about 50%.

The most important observation was, however, that the number of lethal emboli was lowest among the dextran-treated patients. This stresses the importance of flow, which is not enhanced with heparin, but is with dextran 70, and more so with dextran 40.

Our experimental data definitely favor the idea that maintenance of a high venous flow rate is more important than anticoagulation to have prophylaxis of pulmonary embolism, and a combination of prophylactic measures could result in an improved measure of preventing this, despite all, often fatal complication.

Dr. Donald Silver (Columbia, Missouri): I rise to congratulate these authors upon their work, which suggests that low-dose heparin may not reduce the incidence of pulmonary embolism in patients requiring major amputations or hip surgery. However, it has been amply documented that low-dose heparin does reduce the incidence of thrombosis in these patients and probably also reduces the incidence of pulmonary thromboembolism; therefore we give it to "high risk" patients.

I wish to call to the Association's attention a disorder that we have reported in eight patients, recently seen in five more patients, and have had personal communications about five other patients from other institutions. This disorder occurs in a few patients that receive heparin for more than six to eight days. These patients develop heparin-dependent platelet aggregating antibodies which cause widespread platelet aggregation and platelet depletion and have micro- and macrothrombi. These patients have had bleeding and thrombotic complications, with the thrombotic complications including pulmonary embolism, myocardial infarction and even aortic thromboses. This disorder can be disastrous in these already high-risk patients that are receiving heparin. It gets continually worse until the heparin is stopped and other forms of anticoagulation instituted.

The disorder may be recognized first by an increasing requirement of heparin to maintain "adequate" levels of anticoagulation; second by a low platelet count, in the 5000–40,000/mm^3 range, and third, unusual thrombotic or hemorrhagic complications during the heparin therapy.

We now monitor platelet numbers as well as the activated partial thromboplastin time in all patients that we give heparin to on the surgical service at the University of Missouri.

I would like to ask the authors two questions. First, have they recognized this disorder in any of their patients? Second, and more pertinent to the paper, did they differentiate among the types of amputations that were done? For instance, were the amputations performed on patients with traumatic injuries to their limbs, with gangrenous limbs, or with limbs containing thromboses prior to the amputation? The basic question is, perhaps, did the thrombosis occur not because of failure of the "prophylactic" heparin, but because of the administration of an inadequate amount of therapeutic heparin?

DR. JAMES W. WILLIAMS (Closing discussion): When we initiated the study, we made the hypothesis—whether it's correct or not I don't know—that the incidence of fatal pulmonary embolism should be related to the total incidence of pulmonary embolism. This is similar to the hypothesis that is made that the incidence of venous thrombosis in the leg is related to the incidence of pulmonary embolism. Although that hypothesis has never really been proved, particularly with regard to the venous thrombi which develop in the calf, nevertheless, we felt that we were more closely approaching the problem, epidemiologically at least, by measuring as accurately as possible the incidence of pulmonary emboli, whether it was symptomatic or not. We then hypothesized that a diminution or a reduction, in the total incidence of pulmonary emboli should be related to a diminution in the incidence of fatal embolism.

One of Dr. Salzman's questions specifically addressed that point. The incidence of autopsy was essentially the same in both groups. However, the incidence of embolism discovered at autopsy was greater in the control group. There were three patients with embolism discovered at autopsy in the control group, and in two of these it was felt to be associated, or causally related, to the patient's death. This leaves us with a little uneasy feeling about saying that the heparin was not effective, but, of course, this is a small number, and does not have any real statistical significance.

The validity of the serial scan findings, I think, we have demonstrated to be high. We arteriogrammed about 60% of the patients who developed defects on serial scans; of this group—60% of the total—the correlation was 90%. The two patients that I mentioned who did not have arteriographically documented embolism were studied three days later. These were small defects, and it is conceivable that the embolus had lysed.

Therefore, I think our method of detection of embolism is unbiased, and I think it is accurate.

Dr. Salzman's points about other methods of prophylaxis are quite cogent. In these patients, who are at extreme risk, who need an effective method of prophylaxis the most, we are left somewhat in the cold. We are about to undertake a study in which the dose of heparin is increased to 15,000 units per day, instead of 10,000 units.

I'm sure that you are aware of the European study data which several authors have alluded to—the international multicenter study conducted by Professor Kakkar—which used 15,000 units of heparin per day. These are international units, to make things a little more confusing. The U.S.P. unit of heparin is about 10–15% more potent than the international unit, and some have suggested, among them Dr. Sol Sherry, that 15,000 units of U.S.P. heparin may require some real investigation before it is used in this country.

The methods of calf compression, electrical stimulation of the calf, which do the things which Dr. Gelin has suggested—that is, disturb the flow of blood in the veins, augment the pulsatile nature of the flow—seem to be, at least initially, very encouraging, and this may provide some help in this situation.

We did not use venous phlebography or radioactively labeled fibrinogen in these patients because the reliability of that radioactive labeled fibrinogen is somewhat suspect in patients requiring extremity surgery, and the contrast venography would be difficult, if not impossible, in a patient undergoing amputation, particularly above-the-knee amputation. We decided in the design of the study to omit those potentially confusing methods of study.

Dr. Blaisdell, I very much appreciated your comments, and we do anticipate using a more potent form of therapy in our future investigations. He alluded to one of the problems that we hoped to circumvent, which is that multicenter international studies are fraught with many difficulties. Among them are incomplete compliance with the protocol; and as the controvery between London and Basel, Switzerland, has indicated, there can be personality as well as methodologic differences.

Dr. Gelin has referred to the use of dextran. He suggested that it was not as much benefit in the orthopedic patient, but in the general surgical patient it did seem to be effective. Many of us are familiar with this work. We had evaluated the use of dextran in this particular patient, the amputee, and found it not to be of particular benefit.

Dr. Silver's comments were particularly interesting in regard to the exaggerated platelet aggregation associated with the use of heparin. Many authors have reported thrombocytopenia associated with the use of heparin in some patients. The exact etiology of this is not clear to me. We did not see this in our patients. We didn't see any bleeding complications to speak of in either group of patients.

Dr. Silver raised an interesting question. That is: "What were the reasons for doing the amputation, and what was the state of the leg at the time?" In this work, and in work previously done, we found that in the leg to be amputated the incidence of venous thrombosis established approximates 15%, and these patients have an excessively high risk of pulmonary embolism. In our first study it was almost 100%, and in this group it is 50%. The point he is making is that the dose of heparin should be therapeutic, instead of the doses we are calling prophylactic, and so might be more meaningful for these patients.

We have been reluctant to do that because of the complications of hematoma in the amputated ischemic stump, but this certainly bears looking into.

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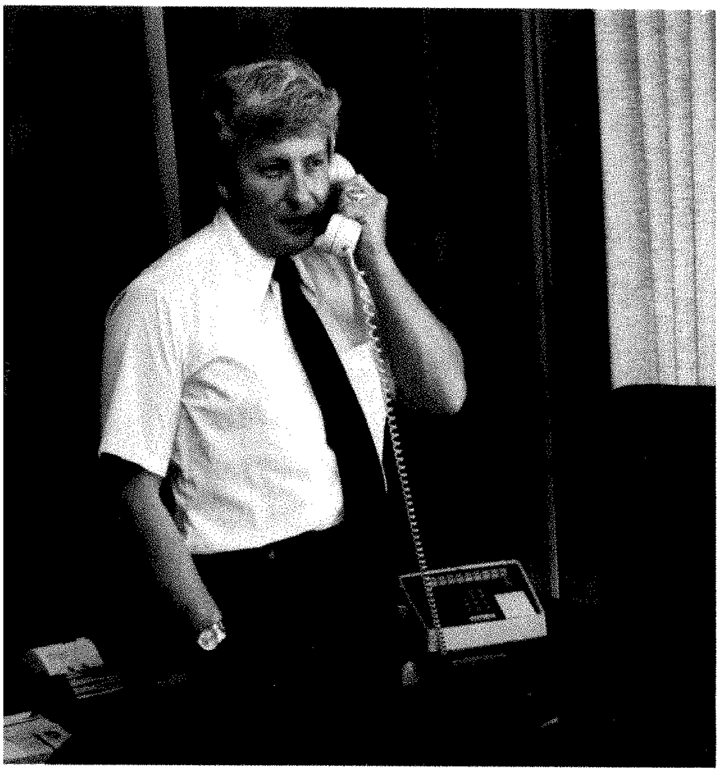

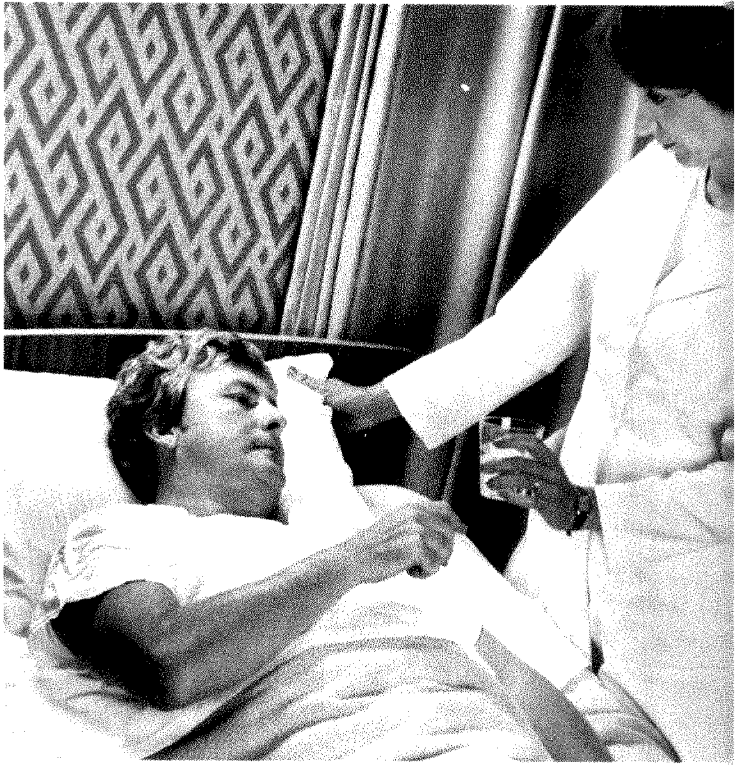

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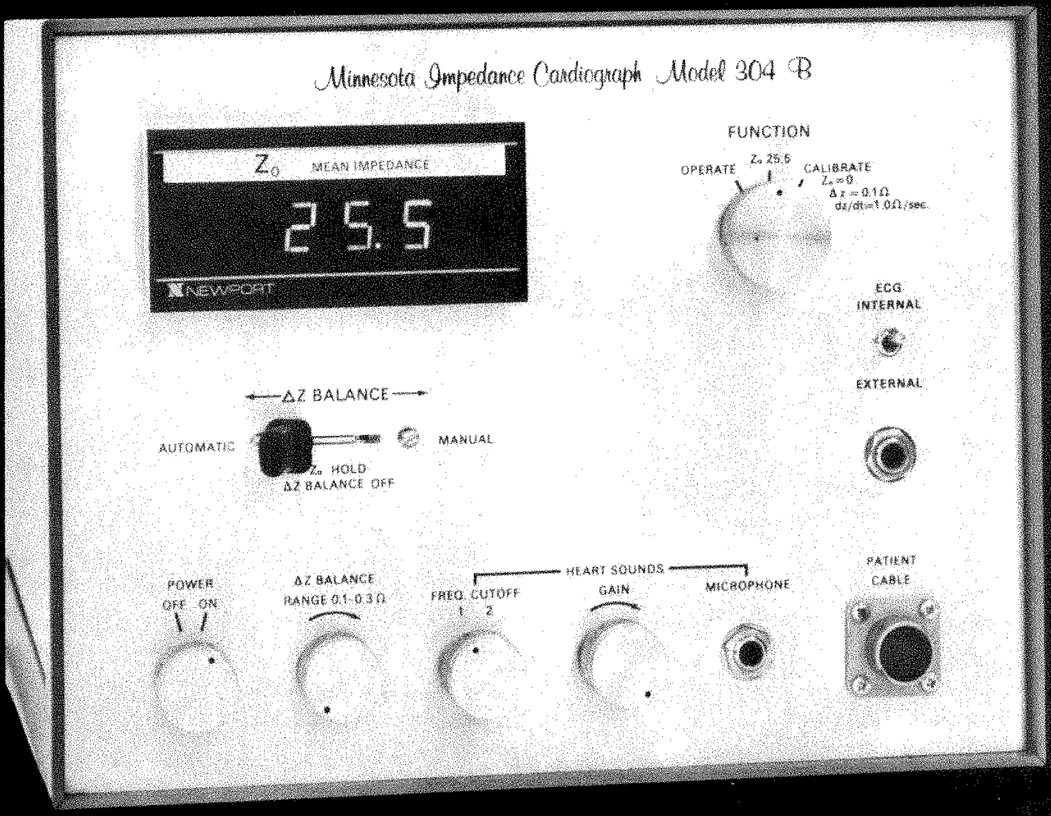

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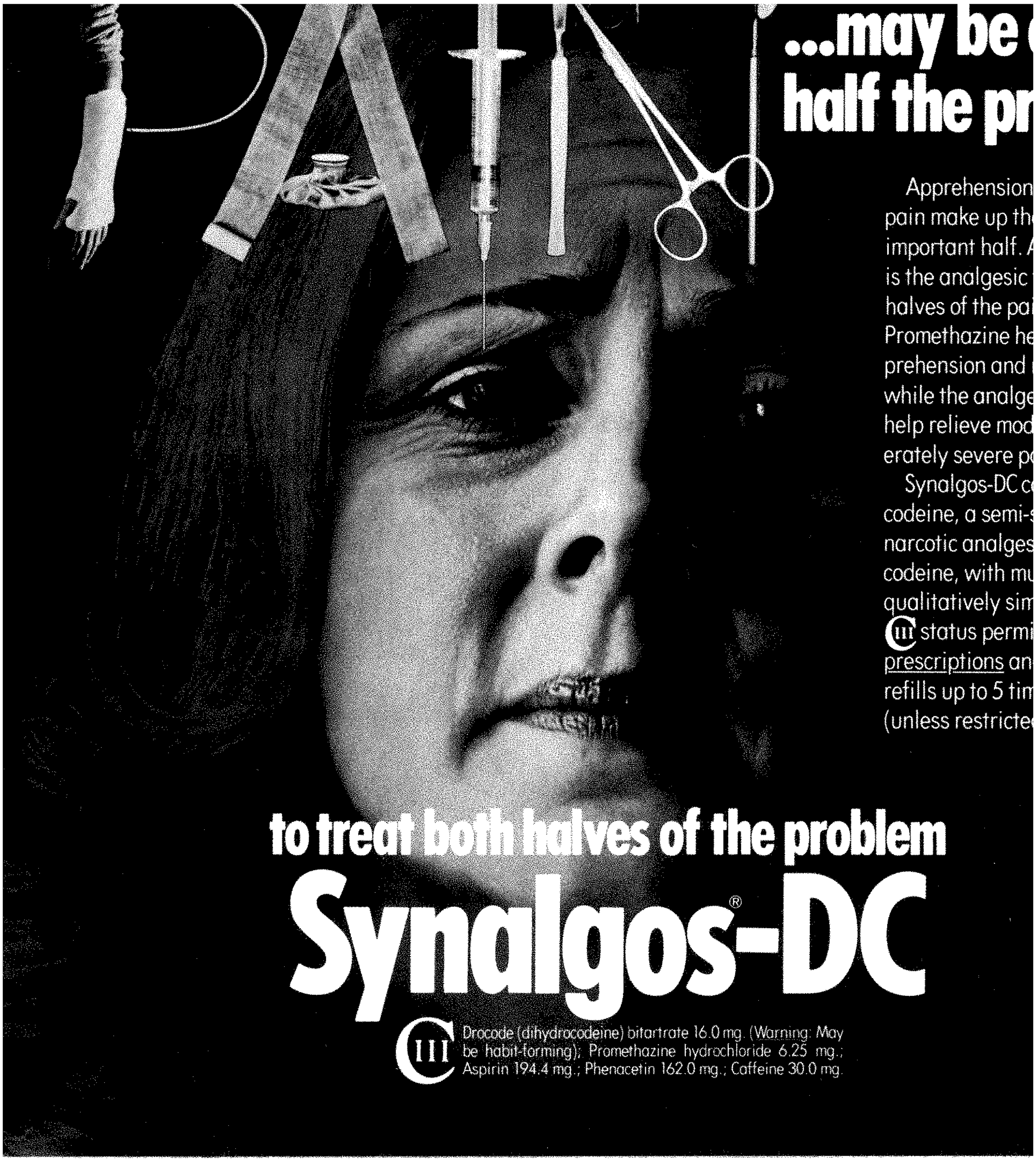
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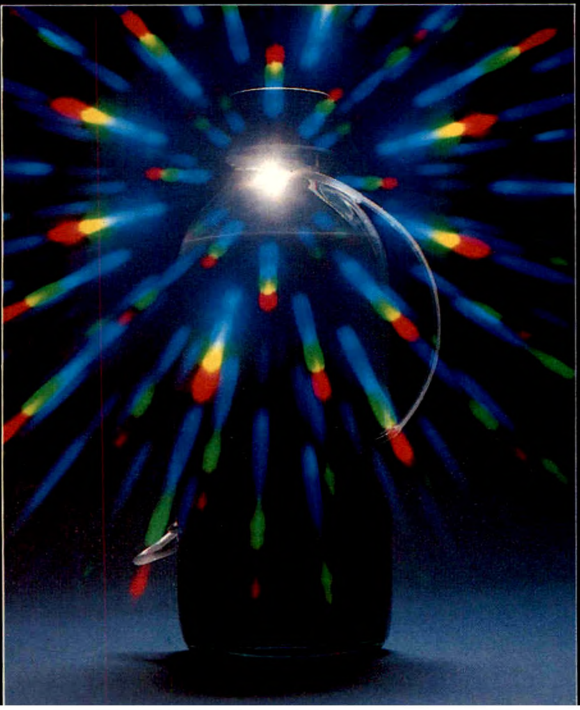

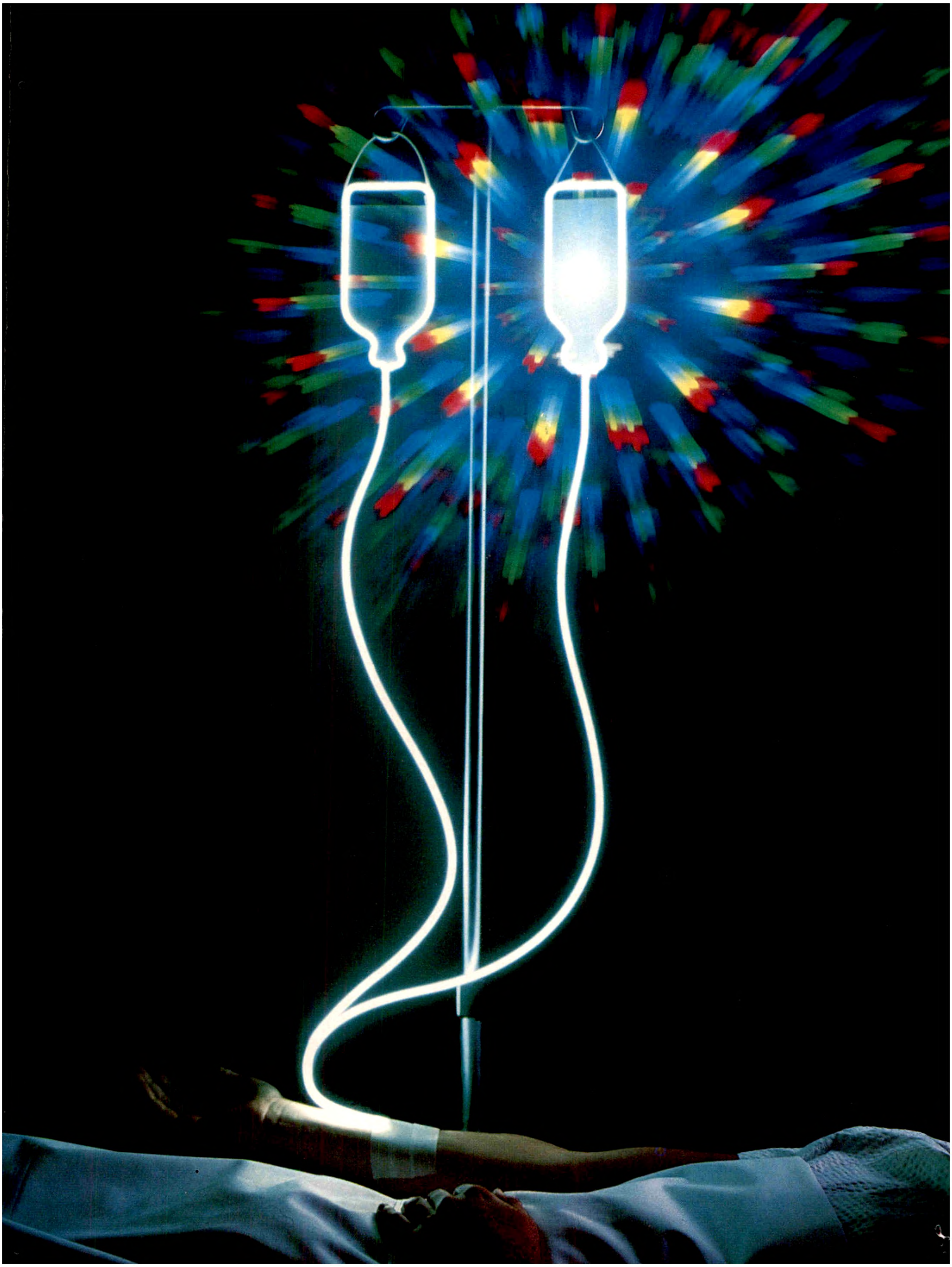

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Intralipid® 10% (10% Intravenous Fat Emulsion) is a fat emulsion prepared for intravenous administration. It is made up of 10% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and Water for Injection. In addition, Sodium Hydroxide has been added to adjust the pH to between 5.5 and 9.0.

The soybean oil is a refined natural product consisting of a mixture of neutral triglycerides of predominantly unsaturated fatty acids. The major component fatty acids are linoleic (54%), oleic (26%), palmitic (9%) and linolenic (8%).

Intralipid® 10% (10% Intravenous Fat Emulsion) has an osmolarity of approximately 280mOsm/liter and contains emulsified fat particles of approximately 0.5 micron size.

The total caloric value, including fat, phospholipid and glycerol, is 1.1 calories per ml. of Intralipid® 10% (10% Intravenous Fat Emulsion).

ACTIONS

Intralipid® 10% (10% Intravenous Fat Emulsion) is metabolized and utilized as a source of energy causing an increase in heat production, decrease in respiratory quotient and increase in oxygen consumption following its administration. The infused fat particles are cleared from the blood stream in a manner thought to be comparable to the clearing of chylomicrons.

Intralipid® 10% (10% Intravenous Fat Emulsion) will prevent the biochemical lesions of essential fatty acid deficiency (EFAD), and correct the clinical manifestations of the EFAD syndrome.

INDICATIONS

Intralipid® 10% (10% Intravenous Fat Emulsion) is indicated as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than five days) and as a source of essential fatty acids when a deficiency occurs.

CONTRAINDICATIONS

The administration of Intralipid® 10% (10% Intravenous Fat Emulsion) is contraindicated in patients with a disturbance of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis and acute pancreatitis if accompanied by hyperlipemia.

Intralipid® 10% (10% Intravenous Fat Emulsion) must not be mixed with electrolyte or other nutrient solutions; no additives can be placed in the bottle of Intralipid® 10%. It is supplied in single dose containers; a partly used bottle must not be stored for later use.

Filters should not be used with Intralipid® 10% (10% Intravenous Fat Emulsion).

Do not use any bottle in which there appears to be an oiling out of the emulsion.

WARNINGS

Caution should be exercised in administering Intralipid® 10% (10% Intravenous Fat Emulsion) to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders, or when there is danger of fat embolism.

PRECAUTIONS

When Intralipid® 10% (10% Intravenous Fat Emulsion) is administered, the patient's capacity to eliminate the infused fat from the circulation must be monitored. The lipemia must clear between daily infusions.

During long term intravenous nutrition with Intralipid® 10% (10% Intravenous Fat Emulsion), liver function tests should be performed; and if these tests indicate that liver function is impaired, the therapy should be withdrawn.

Frequent (some advise daily) platelet counts should be done in neonatal patients receiving parenteral nutrition with Intralipid® 10% (10% Intravenous Fat Emulsion).

Cutter Medical
Division of Cutter Laboratories, Inc.
Berkeley, California 94710

ADVERSE REACTIONS

The adverse reactions observed can be separated into two classes:

1. Those more frequently encountered which are due either to contamination of the intravenous catheter and result in sepsis, or to vein irritation by concurrently infused hypertonic solutions and may result in thrombophlebitis. These adverse reactions are inseparable from the hyperalimentation procedure with or without Intralipid® 10% (10% Intravenous Fat Emulsion); and
2. Those less frequent reactions more directly related to Intralipid® 10% (10% Intravenous Fat Emulsion) which are: a) **immediate or early adverse reactions**, each of which has been reported to occur, in clinical trials, in an incidence of less than 1%: dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness and irritation at the site of infusion, and rarely thrombocytopenia in neonates. b) **delayed adverse reactions**: hepatomegaly, splenomegaly, thrombocytopenia, leucopenia, transient increases in liver function tests, and over loading syndrome (focal seizures, fever, leukocytosis, splenomegaly and shock).

The deposition of a brown pigmentation in the reticuloendothelial system, the so-called "intravenous fat pigment", has been reported in patients infused with Intralipid® 10% (10% Intravenous Fat Emulsion). The cause and significance of this phenomenon are unknown.

DOSAGE AND ADMINISTRATION

Intralipid® 10% (10% Intravenous Fat Emulsion) should be administered as a part of total parenteral nutrition intravenously via a peripheral vein or by central venous infusion.

Adult Patients The initial rate of infusion in adults should be one ml./minute for the first 15 to 30 minutes of infusion. If no untoward reactions occur (see Adverse Reactions section), the infusion rate can be increased so that 500 ml. will be infused over a period of four hours. Only 500 ml. of Intralipid® 10% (10% Intravenous Fat Emulsion) should be infused into adults on the first day of therapy. If the patient has no untoward reactions, the dose can be increased on the following day. The daily dosage should not exceed 2.5 g./kg. of body weight. Intralipid® 10% should make up no
more than 60% of the total caloric input of the
tient. Carbohydrate and a source of amino ac
should comprise the remaining 40% or more
the caloric input.

Pediatric Patients The initial rate of infusion
pediatric patients should be 0.1 ml./minute
the first 10 to 15 minutes. If no untoward reacti
occur, the rate can be increased to permit i
sion of 1 g./kg. in four hours. The daily dos
should not exceed 4 g./kg. of body weight.
tralipid® 10% (10% Intravenous Fat Emulsi
should make up no more than 60% of total cal
input of the patient. Carbohydrate and a sou
of amino acids should comprise the remain
40% or more of the caloric input.

Fatty Acid Deficiency When Intralipid® 10% (
Intravenous Fat Emulsion) is administered to
rect fatty acid deficiency, eight to ten percen
the caloric input should be supplied by
tralipid® 10% in order to provide an adequ
amount of linoleic acid to correct the deficien

Administration Intralipid® 10% (10% Intraven
Fat Emulsion) should be infused separately f
any other intravenously administered solution
order to avoid disturbing the stability of the e
sion. It must not be mixed with electrolyte
other nutrient solutions, and drugs or vitam
must not be added to the emulsion in the infus
bottle. It can be infused into the same periph
vein as the carbohydrate-amino acids solut
by means of a Y-connector located near the i
sion site, and flow rates of each solution sh
be controlled separately by infusion pumps. Fi
should not be used with Intralipid® 10% emuls

A special Intralipid® 10% (10% Intravenous
Emulsion) intravenous administration se
available.

Intralipid® 10% (10% Intravenous Fat Emuls
is supplied in single dose containers; the rem
ing contents of a partly used bottle must not
stored for later use.

STORAGE

Intralipid® 10% should be stored under re
eration at 4° to 8° C.

Do not freeze Intralipid® 10% (10% Intraven
Fat Emulsion); if accidentally frozen, discard b

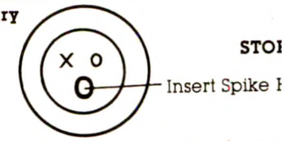
HOW SUPPLIED

Intralipid® 10% (10% Intravenous Fat Emuls
is supplied as a sterile emulsion in 500
containers.

IMPORTANT
ADDITIONAL PRODUCT INFORMATION

Read Carefully Before Administration o
Intralipid® I.V. Fat Emulsion

1. Stopper Entry



a. Be sure to swab the face of the stoppe
mediately before piercing.
b. Insert spike through the largest circle o
pared stopper with a straight thrust and
twist to fully seat spike.

**2. Special Intralipid® I.V. Fat Emulsion Ad
istration Set**

A special Intralipid® I.V. Fat Emulsion admin
tion set is provided with each bottle. Co
tional administration sets contain poly
chloride (PVC) components that contain
(Diethyl Hexyl Phthlate) as a plasticizer. Fat
taining fluids such as Intralipid® extract
from these PVC components.

The special Intralipid® I.V. Fat Emulsion set
not contain DEHP. Therefore, this specia
should be used for the administration
tralipid® 10% (Intravenous Fat Emulsion).

When we told surgeons that our new Generation II single-use instruments get used, not everybody believed us.

Perhaps they remembered the earlier days when single-use special procedures instruments didn't always perform to expectations. Perhaps they demanded too much from single-use instruments.

Now, they can demand all they want. Generation II is ready to meet all challenges—and challengers.

Our Generation II scissors cut, especially at the tips. Our Generation II hemostats hold, without overbiting. Our Generation II needle holders grip, without slippage.

When you need a sterile-packed, single-use instrument in the ER or on your rounds, Acme United Generation II instruments and trays might be the best things you can put your hands on. Choose from 16 well-made instruments, in 22 different tray configurations. We can also put up special dressing trays to suit your particular needs and specifications.

That Acme United Generation II single-use instruments cut risk of cross contamination, pilferage, and liability, and cost a tenth the price of reusables is impressive. That they work well is imperative. We'll be pleased to send you some samples.

Ask your nurse to call our toll free number, (800) 243-9852, or write to Acme United Corporation, Medical Products Division, Bridgeport, Conn. 06609.

Acme United GENERATION II
Single-use instruments that get used.

Acme United Corporation
Medical Products Division

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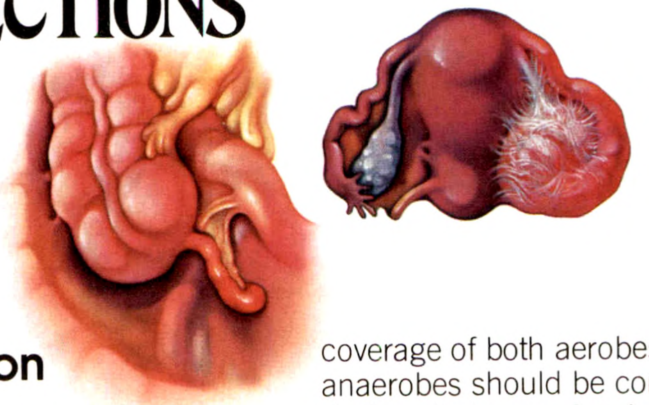
THE BIPHASIC NATURE OF SERIOUS INTRA-ABDOMINAL/PELVIC INFECTIONS



Introduction

The biphasic clinical nature of serious intra-abdominal and female pelvic infections may be related to sequential dominance first of aerobes and then of anaerobes. Antimicrobial coverage of both aerobes and anaerobes should be considered during all stages of serious intra-abdominal and female pelvic infections.

The majority of these infections are polymicrobial. During the early, toxic phase, aerobes are

Acute Phase:
Peritoneal Response

Peritoneal contamination with polymicrobial (aerobic and anaerobic) flora from the bowel or vagina may occur during surgery or as a result of trauma, septic abortion, or perforating diseases such as appendicitis.

Clinical signs in the acute phase include increasing abdominal tenderness and fever. Bacteremia, which may progress to septic shock, occurs fairly frequently. In female pelvic infections, bacteremia and septic pelvic thrombophlebitis are always a threat because of the rich vasculature of the female pelvis.

Initially, antimicrobial therapy directed against aerobes such as *Escherichia coli* often results in defervescence and clinical improvement. Failure of the patient to respond or recurrence of symptoms may indicate anaerobic involvement. *B. fragilis* is the anaerobe most frequently isolated in patients with intra-abdominal sepsis or serious female pelvic infections.

Late Phase:
Peritoneal Response

The clinical course may progress to walling off of the infection and subsequent abscess formation. These collections of pus can be located intraperitoneally, retroperitoneally, or within the viscera.

Progression from peritonitis to abscess formation may be an insidious process or may be marked by sudden deterioration of the patient who had been recovering. At this point, failure to respond to appropriate antibiotic therapy should alert the clinician to the possibility of intra-abdominal or pelvic abscess formation and

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generally the dominant pathogens; the coexistent anaerobes may contribute to the clinical picture. In the patient who progresses to the late phase and develops an abscess, anaerobes (especially *Bacteroides fragilis*) are the dominant isolates.

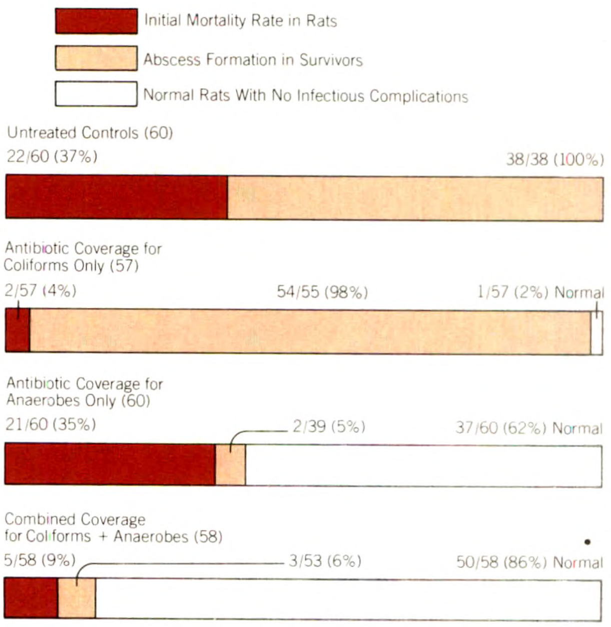
the potential need for operative intervention.

In both the early peritonitis stage and the later abscess stage, culture of purulent material yields aerobes and anaerobes in the majority of instances. In fact, anaerobes have been isolated from 90% to 96% of intra-abdominal infections associated with bowel perforation. Anaerobes such as *B. fragilis* have been isolated in 80% to 100% of patients with pelvic abscesses studied with appropriate techniques of specimen collection and culture.

INDUCED PERITONEAL SOILAGE

The sequence of events that follow experimental induction of peritoneal soilage in rats parallels the biphasic course of this disease. Although animal data cannot be directly applied to humans, this model helps explain the pathogenesis.

A standardized inoculum of rat colonic contents containing both aerobic and anaerobic organisms was implanted into the peritoneal cavity of male Wistar rats. The animals were observed for response and survivors were sacrificed after ten days. The rats developed a two-stage disease: initial, acute peritonitis and later, intra-abdominal abscesses. Mortality and progression of these stages varied sharply with antimicrobial coverage for aerobes, anaerobes, or both.



In this study, coliform organisms appeared to be responsible for the early mortality associated with fecal peritonitis, whereas *B. fragilis* and other anaerobes were associated with later abscess formation.

For information about one antibiotic to consider in treating serious infections due to anaerobic pathogens, please turn the page.

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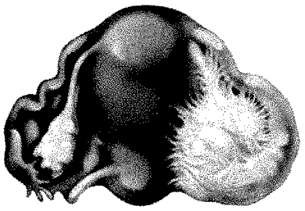
THERAPEUTIC CONSIDERATIONS...

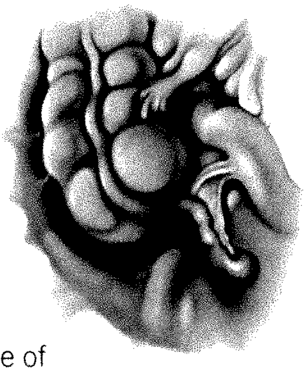


Anaerobic activity

Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal and female pelvic infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection; serious lower respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; and serious skin and soft-tissue infections caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, in vitro dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).



Indications include: serious lower respiratory tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances, the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible in vitro and were successfully eradicated from the clinical lesions.

Other therapeutic considerations

1. Cleocin PO_4 (clindamycin phosphate injection) is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section of the brief summary on the following page.

> If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

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*Clostridia are more resistant than most anaerobes to clindamycin. Some species, eg, *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:
clindamycin phosphate
equivalent to .... 150 mg clindamycin base
benzyl alcohol .... 5 mg
disodium edetate .... 0.5 mg
water for injection .... qs
When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative. MED B-5-S J-6219-9

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

Ready when you need it.
1 Disposable Syringe with sterile 22 gauge, 1-1/4 inch needle
Compazine® Injection (2 ml.=10 mg.)
brand of prochlorperazine
For deep I.M. or I.V. administration
NDC 0007-0C51-01
Do not use entire contents for children — See dosage instructions
10 mg. (2 ml.=10 mg.)
Bend back to open
10 mg. (2 ml.=10 mg.)
LOT 153
EXP: 5/1
COMPAZINE
BRAND OF

'Compazine' controls vomiting.

- Unsurpassed antiemetic action
- 12 dosage forms and strengths

NOTE: Do not use 'Compazine' in pediatric surgery. Not recommended for children under 20 lbs. or 2 years of age. In children with acute illnesses or dehydration, use only under close supervision.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications: Management of the manifestations of psychotic disorders; management of psychoneurotic patients displaying primarily symptoms of moderate to severe anxiety and tension; and for control of severe nausea and vomiting.

'Compazine' has not been shown effective in the management of behavioral complications in patients with mental retardation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings: The extrapyramidal symptoms which can occur secondary to 'Compazine' may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of 'Compazine' and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: The antiemetic action of 'Compazine' may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (See WARNINGS). Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. Patients on long-term therapy, especially high doses, should be evaluated periodically for possible adjustment or discontinuance of drug therapy. **In children with acute illnesses or dehydration, use only under close supervision.**

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

Supplied: Tablets—5, 10 and 25 mg., in bottles of 100; Spansule® capsules—10, 15, 30 and 75 mg., in bottles of 50; Injection—5 mg./ml. in 2 ml. ampuls, 10 ml. vials, and 2 ml. disposable syringes; Suppositories—2½, 5 and 25 mg.; Syrup—5 mg./5 ml.; Concentrate (intended for institutional use only)—10 mg./ml.; Single Unit Packages of 100 (intended for institutional use only)—5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

Compazine® brand of prochlorperazine Injection: 5 mg./ml.

the emesis nemesis

SK&F
a SmithKline company

Smith Kline &French Laboratories Philadelphia, PA

When vitamin B-complex with C is indicated

5 4 REASONS TO PRESCRIBE BEROCCA® TABLETS

Rx only

Balanced formula **1** High potency B-complex with 500 mg vitamin C tablets for patients such as those with chronic disease, febrile illness or GI disorders, and surgical patients or heavy drinkers.

Better patient compliance **2** The specific instructions accompanying a prescription may encourage patients to adhere to the regimen *you* recommend.

Virtually no odor or aftertaste **3** Eliminates these unpleasant characteristics often associated with B-complex with C products.

Low cost **4** Economically priced; costs no more than many other brands.

Rx only

Rx only guarantees your involvement in *total* patient management. In addition, with Rx only the patient may qualify for third-party reimbursement.

Please see complete product information, a summary of which follows:

Each Berocca Tablet contains:

Thiamine mononitrate (Vitamin B_1)	15 mg
Riboflavin (Vitamin B_2)	15 mg
Pyridoxine HCl (Vitamin B_6)	5 mg
Niacinamide	100 mg
Calcium pantothenate	20 mg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Folic acid	0.5 mg
Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

Dosage: 1 or 2 tablets daily, as indicated by clinical need.

Available: In bottles of 100 and 500.

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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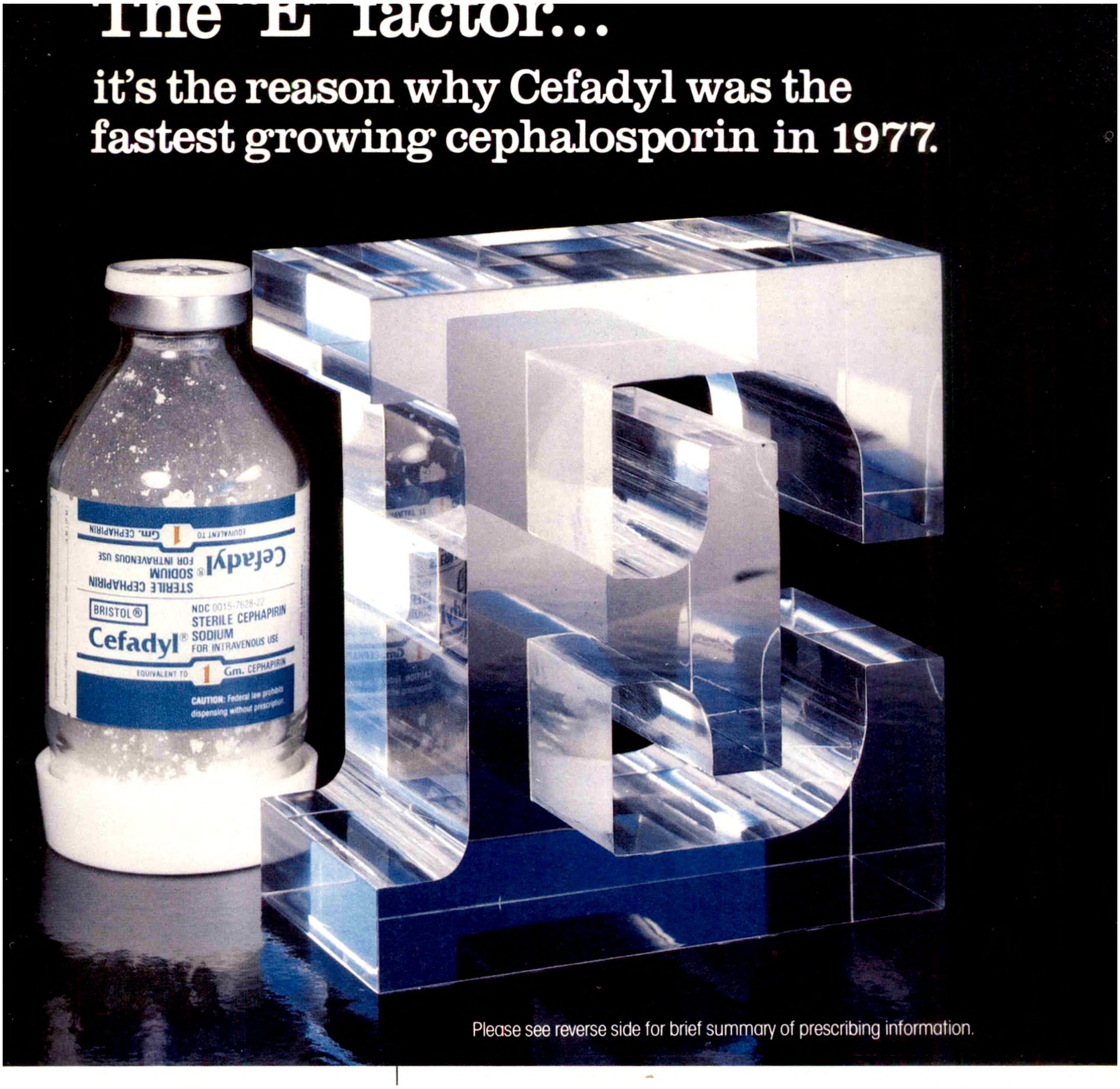
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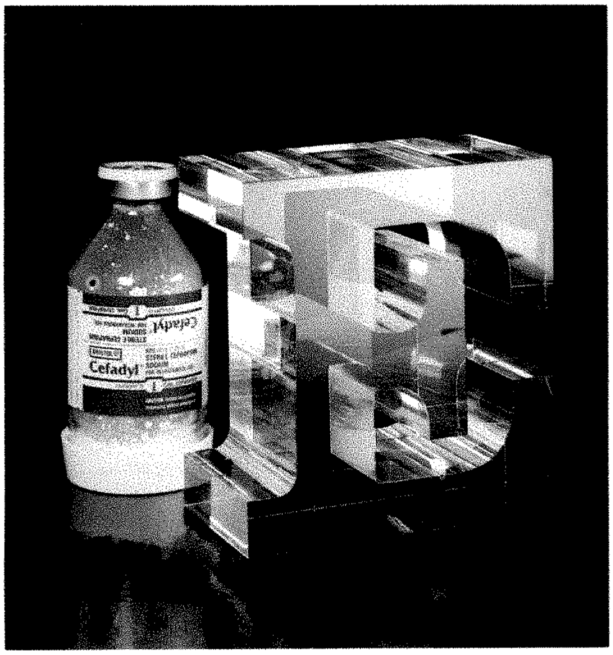

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Abdominosacral Resection for Carcinoma of the Midrectum: Ten Years Experience

S. ARTHUR LOCALIO, KENNETH ENG, THOMAS H. GOUGE, JOHN H. C. RANSON

Abdominosacral resection allows curative resection of midrectal cancer with excellent preservation of sphincter function. In the last ten years 427 patients underwent resection for rectal carcinoma at University Hospital by one surgeon. (SAL) The operation, selected by preoperative sigmoidoscopic measurement, was anterior resection (AR) in 239, abdominosacral resection (ASR) in 100, and abdominoperineal resection (APR) in 88. Operative mortality was 1.7% for AR, 2% for ASR and 2.3% for APR. All patients were completely continent of stool and flatus after AR and ASR. Follow-up is complete in 194 of 195 patients treated five to ten years ago. Five year survival for curative resection (no distant metastases) was 67.3% after AR (66/98), 58.3% after ASR (21/36), and 50% after APR (15/30). For patients without tumor in lymph nodes, survival rates were 78.3% for AR, 64.3% for ASR and 63.2% for APR. With involvement of regional nodes, survival fell to 41.4% for AR, 37.5% for ASR and 27.3% for APR. For lesions at 5–8.5 cm, five year survival was 61.1% for ASR and 58.3% for APR. No statistical difference in survival time was noted when patients were matched for age, sex, level of lesion and extent of spread. Pelvic recurrences were detected in 16.7% after ASR, 15.3% after AR and 33.3% after APR. All of the pelvic recurrences after ASR and the majority of those after AR and APR occurred in patients with tumor invasion of perirectal fat. These data strongly support the applicability of ASR as an important advance in the treatment of midrectal cancer. Although technically demanding, ASR has permitted preservation of anal continence without sacrifice of long-term cure in approximately 50% of patients who would otherwise have required APR.

THE CHOICE OF OPERATION for cancer of the rectum remains controversial. Anterior resection (AR) is an accepted procedure for lesions in the upper third of the rectum. Below this level abdominoperineal resection (APR) is generally performed.

Our early results suggested that abdominosacral resection (ASR) is a safe and effective operation for the treatment of midrectal cancer with reliable preservation of continence.[9]

This report presents further experience with ASR and compares long-term results of this operation with those of parallel series of AR and APR.

From The Department of Surgery, New York University Medical Center, New York, New York

Materials and Methods

From 1966 to 1976, 427 patients underwent operation for adenocarcinoma of the rectum by one surgeon (SAL). The operation was AR in 239, ASR in 100 and APR in 88.

Selection of operation and surgical techniques have been previously described in detail.[8,10] Men with lesions 7–11 cm from the anal verge and women with lesions at 5.5–10 cm were candidates for ASR. All measurements were made by two observers using sigmoidoscopy; the patient was in the knee chest position. The distances were measured from the mucocutaneous junction to the lowest gross extension of the tumor.

Patients scheduled for ASR were explored in the lateral position. In 22 ASR patients, after mobilization of the rectum, it was possible to complete the operation with satisfactory margins by AR. In two patients, ASR was abandoned because of the inability to obtain an adequate distal margin; instead, an APR was therefore performed.

Data on age, sex, site of growth, and Dukes' classification are summarized in Tables 1 and 2. The APR group consisted of more men, more Dukes' C lesions and the lowest tumors. These factors have been shown to adversely affect prognosis. The preponderance of men in the APR group is not surprising since the wider female pelvis allows resection with anastomosis at a lower level.

Operative mortality and morbidity and functional results were studied in all 427 patients. Long-term survival rates and pelvic recurrence rates were determined in the 195 patients treated from 1966 to 1971. Follow-up was by regular office visits supplemented by telephone calls to referring physicians. Follow-up was complete in 194 of 195 patients treated before 1971.

Results

Operative Mortality

There were four early deaths (1.7%) after AR, two (2%) after ASR and two (2.3%) after APR (Table 3).

Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

Reprint requests: S. Arthur Localio, M.D., Department of Surgery, New York University Medical Center, 550 First Avenue, New York, New York 10016.

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TABLE 1. *Sex, Age, Site of Growth and Operation in 427 Patients with Rectal Cancer (1966–1976)*

Operation	Number, Sex	Age (Yrs.)	Site of Growth (cm from Anal Verge)
Anterior Resection	121 M, 118 F 239	23–92 Mean 63.7	above 7.5 Mean 13.2
Abdominosacral Resection	53 M, 47 F 100	39–85 Mean 61.5	5.5–11 Mean 8.3
Abdominoperineal Resection	60 M, 28 F 88	32–86 Mean 63.6	1–8.5 Mean 5

Anastomotic Complications

Two anastomotic leaks were detected in 239 patients undergoing AR. Out of 100 patients undergoing ASR 12 developed anastomotic leaks. In eight of the 12 this resulted in a well controlled posterior fistula, but four patients had peritoneal signs and required emergency colostomy. One of the two early deaths after ASR was due to fecal peritonitis.

Anastomotic complications occurred more frequently in men (15%) than in women (8.5%). In the first 50 patients undergoing ASR, the leak rate among men 60 years or younger was 37.5%. Accordingly, in seven of 14 other men under 65 years, cecostomy (four) or diverting colostomy (three) was done at the time of primary operation. No anastomotic leaks occurred in these seven patients, but two of seven unprotected patients developed anastomotic leaks requiring secondary colostomy. There was no correlation between age and leak rate in women.

Continence

All patients were continent of stool and flatus after ASR and AR. Reservoir function was temporarily impaired, and patients usually complained of frequent small bowel movements in the early postoperative period. Aberrant bowel habits were generally more pronounced after ASR, but the ultimate functional result was indistinguishable from that following AR.

Long-term Survival

Of the 195 patients treated between 1966 and 1971, five operative deaths and 26 palliative resections were excluded, leaving 164 patients for analysis. One patient was lost to follow-up after AR and was assumed dead.

The crude five-year survival rate for curative operations was 67.3% for AR, 58.3% for ASR and 50% for APR (Table 4). For patients with no tumor in lymph nodes, survival rates were 78.3% for AR, 64.3% for ASR and 63.2% for APR. With tumor in regional nodes, survival fell to 41.4% for AR, 37.5% for ASR and 27.3% for APR.

Cause of late death. Recurrent cancer accounted for 76.9% of the late deaths after AR, 72.2% after ASR and 81.8% after APR.

Sex. Five-year survival rates for 74 women in this series was 64.9% and for 90 men it was 60%. Women also fared better than men after ASR, five year survival being 68.8% in women and 50% in men.

Site of Growth

In order to arrive at a more closely matched group of patients with midrectal cancer, patients undergoing APR for lesions below 5 cm and ASR for lesions above 8.5 cm were eliminated. This yielded 12 APR and 18 ASR for lesions at 5–8.5 cm. The characteristics of the two groups and their five year survival rates are presented in Table 5. Five year survival rates after ASR and APR for midrectal cancer were comparable. For the lowest lesions, ASR did not decrease the patients' chance for cure.

Survival time was also studied, in an attempt to uncover a difference between ASR and APR. A series of matched pairs were drawn, with one member of the pair selected from the 12 patients who underwent APR and the other from the ASR group.

The variables on which the two groups were matched included sex, age, level of lesion, size of lesion and Dukes' classification. Matched pairs were created serially with two, three and then four variables. From this small sample, there was no evidence to suggest that patients who had undergone ASR had any decrease in the postoperative life expectancy.

TABLE 2. *Dukes' Classification and Operation of 427 Rectal Cancers (1966–1976)*

	Dukes' Class								
	A		B		C		Palliative		
Operation	No.	%	No.	%	No.	%	No.	%	Total
Anterior Resection	75	31.3	69	28.9	55	23.0	40	16.7	239
Abdominosacral Resection	37	37	23	23	30	30	10	10	100
Abdominoperineal Resection	29	32.9	14	15.9	36	40.9	9	10.2	88

TABLE 3. *Anastomotic Leaks and Deaths in 427 Patients with Rectal Cancer (1966–1976)*

Operation	No. Patients	Anastomatic Leaks: Fistula	Anastomatic Leaks: Peritonitis	Total	Deaths
Anterior Resection	239	0	2	2 (0.8%)	4 (1.7%)
Abdominosacral Resection	100	8	4	12 (12%)	2 (2%)
Abdominoperineal Resection	88	—	—	—	2 (2.3%)

TABLE 4. *Crude Five Year Survival Rate of 164 Curative Resections (1966–1971)*

Operation	No. Patients		Five Year Survivors		% Five Year Survival	
Anterior Resection						
Without lymphatic metastases	69		54		78.3	
With lymphatic metastases	29		12		41.4	
Total		98*		66		67.3
Abdominosacral Resection						
Without lymphatic metastases	28		18		64.3	
With lymphatic metastases	8		3		37.5	
Total		36		21		58.3
Abdominoperineal Resection						
Without lymphatic metastases	19		12		63.2	
With lymphatic metastases	11		3		27.3	
Total		30		15		50

* One patient was lost to followup and considered dead of disease.

Pelvic Recurrence

Another measure of the efficacy of a cancer operation is its success in controlling local disease. Pelvic recurrence after ASR occurred in six patients (16.7%), an incidence which is comparable to AR (15.3%) and lower than that for APR (33.3%) (Table 6). All of the pelvic recurrences after ASR and the majority of those after APR and AR occurred in patients with tumor invasion of perirectal fat. Patients undergoing ASR did not run a greater risk of local recurrence.

Discussion

APR and AR are well established methods for treatment of cancer of the rectum. Pathologic and experimental studies of the lymphatic and local spread of rectal cancer have established the rationale for sphincter-saving resection of lesions in the midrectum.[3,4,12,15] Several large series have demonstrated the adequacy of various pull-through operations in terms of cure rate, but the functional results have been inconsistent.[2,6,17]

ASR affords the same scope of resection as other sphincter saving operations. The transsacral approach first described by Kraske is a logical means for restoring intestinal continuity. Direct posterior exposure of the distal limit of resection allows accurate construction of an anastomosis at the level of the levators without disturbing anorectal structures and their innervation.

ASR has been followed by essentially normal sphincter function in 100 consecutive patients. All patients were completely continent of stool and flatus. Temporary loss of reservoir function led to frequent bowel movements in the early postoperative period, but normal bowel habits generally returned within 12 weeks. The process of adaptation is facilitated by early institution of a diet high in fiber and moisture, and by encouraging the patient to suppress the frequent urge to defecate.

Anastomotic leak remains a serious danger in all low rectal anastomoses, particularly after ASR. In this series, pelvic drains were virtually never used. Some subclinical leaks after AR were undoubtedly overlooked. Following ASR, the close proximity of the sacral wound to the anastomosis allows easy egress of fecal material, and the detection rate for small leaks is probably higher. These leaks usually resulted in well controlled fecal fistulae. Nonetheless, four patients required emergency operation for fecal peritonitis and one died. Our early experience showed that anastomotic leak was particularly likely in men under 65 years,

TABLE 5. *Crude Five Year Survival Rate of 30 Patients with Lesions at 5.0–8.5 cm*

Operation	No. Patients		Sex	Site of Growth	Five Year Survival	
Abdominosacral Resection			11 M, 7 F	5.5–8.5 cm Mean 7.7 cm		
Without lymphatic metastases	11				8 (72.7%)	
With lymphatic metastases	7				3 (42.9%)	
Total		18				11 (61.1%)
Abdominoperineal Resection			10 M, 2 F	5.0–8.5 cm Mean 6.4 cm		
Without lymphatic metastases	8				5 (62.5%)	
With lymphatic metastases	4				2 (50%)	
Total		12				7 (58.3%)

TABLE 6. *Pelvic Recurrences in 164 Curative Resections (1966–1971)*

Operation	No. Patients Treated	No. Pelvic Recurrences	% Pelvic Recurrences
Anterior Resection			
Total	98	15	15.3
Without fat invasion	44	2	4.5
With fat invasion	54	13	24.1
Without lymphatic metastases	69	9	13.0
With lymphatic metastases	29	6	20.6
Abdominosacral Resection			
Total	36	6	16.7
Without fat invasion	24	0	0.0
With fat invasion	12	6	50.0
Without lymphatic metastases	28	2	7.1
With lymphatic metastases	8	4	50.0
Abdominoperineal Resection			
Total	30	10	33.3
Without fat invasion	13	3	23.1
With fat invasion	17	7	41.2
Without lymphatic metastases	19	6	31.6
With lymphatic metastases	11	4	36.4

and proximal colostomy was recommended in this group. Subsequently, in seven men under 65, the anastomosis seemed secure and a colostomy was omitted. Anastomotic leak requiring secondary colostomy occurred in two of these seven. Therefore the anastomosis should be protected in young men, even when the conditions for primary anastomosis appear ideal. We continue to perform primary anastomosis alone in women and older men, but would not hesitate to add the protection of a colostomy in individual cases. We believe that the higher leak rate in young men is due to technical difficulties encountered with a narrow pelvis and a thick muscular pelvic diaphragm. The narrow male pelvis also limits the extent of clearance of tumor and probably accounts for poorer survival rates in men.

The expected results of radical resection for carcinoma of the rectum are well documented. Lockhart-Mummery[11] reviewed the records of 3163 patients operated on for primary tumors of the rectum at St. Mark's Hospital from 1948 to 1972. The crude five year survival rate for 1931 patients surviving radical resection for cure was 56.6%. Survival rate was 52.7% after APR and 66.7% after AR. The overall five year survival rate in our series of 164 patients surviving curative resection in 1966–1971 was 62.2%. Survival rate was 50% after APR and 67.3% after AR. The five year survival rate of 58.3% after ASR falls between the rates for APR and AR in this series and in the St. Mark's Hospital series.

The influence of site of growth on prognosis of rectal cancer had long been recognized. Survival rates for high lesions are better than for low lesions in most series. Five year survival rates according to site of growth for APR, ASR or AR in this series is compared to results of AR reported by Waugh and Kirklin,[16] Stearns and Binkley,[14] and Gilbertsen[5] (Table 7). Five year survival rates in our series in which the choice of operation was determined by site of growth is comparable to survival rates achieved by APR for tumors at each level in the other series.

Waugh and Kirklin further distinguished survival rates according to the status of lymph nodes for upper, middle and low rectal lesions. Survival rates for APR reported by these authors, taking in to account nodal metastases and site of growth, are comparable to results of sphincter saving resections in this series. Long-term survival rate after radical resection for cancer of the rectum was affected by the site of growth and the extent of spread, but not by the operation performed.

In assessing the results of ASR, particular attention was paid to the question of local recurrence. The true incidence of local recurrence after radical resection for rectal cancer is difficult to determine except by reoperation or autopsy. Even then it is often impossible to distinguish suture line recurrence from secondary ingrowth from surrounding tissues. For this study, patients were considered to have pelvic recurrence if follow-up revealed tumor at or near the anastomosis, mass in the lower abdomen or pelvis, ureteral obstruction, suspicious lesion in pelvic bone scan or x-ray, para-aortic lymph node defect on lymphangiogram, or sacral nerve pain. The incidence of pelvic recurrence after ASR was comparable to that of AR and lower than that following APR. There was a striking correlation between tumor invasion of perirectal fat and pelvic recurrence in all patients. This pattern of local recurrence has also been observed by others.[1,7,13]

It is hoped that the overall results of treatment of carcinoma of the rectum can be improved by the identification or development of effective local or systemic adjuvant therapy. Since patients with tumor involve-

TABLE 7. *Five Year Survival Rate and Site of Growth of 164 Curative Resections (1966–1971)*

	% Five Year Survival			
Site of Growth	Localio	Waugh & Kirklin	Stearns & Binkley*	Gilbertsen
Lower Rectum				
Abdominoperineal Resection	50%	46.2%	52.8%	44%
Mid Rectum				
Abdominosacral Resection	58.3%	—	—	—
Abdominoperineal Resection	—	51.1%	61.8%	44%
Upper Rectum				
Anterior Resection	67.3%	—	—	—
Abdominoperineal Resection	—	53.8%	72.5%	52.5%

* Death from other causes and patients lost to followup excluded.

TABLE 8. *Five Year Survival Rate, Site of Growth and Status of Lymph Nodes in 164 Curative Resections (1966–1971)*

	% Five Year Survival Rate	
Site of Growth	Localio	Waugh & Kirklin
Lower Rectum		
Abdominoperineal resection		
without lymphatic metastases	63.2	66.0
with lymphatic metastases	27.3	23.3
Mid Rectum		
Abdominosacral resection		
without lymphatic metastases	64.3	—
with lymphatic metastases	37.5	—
Abdominoperineal resection		
without lymphatic metastases	—	75.5
with lymphatic metastases	—	25.0
Upper Rectum		
Anterior resection		
without lymphatic metastases	78.3	—
with lymphatic metastases	41.4	—
Abdominoperineal resection		
without lymphatic metastases	—	68.1
with lymphatic metastases	—	33.3

ment of perirectal fat or lymph nodes have the highest risk of pelvic recurrence, the efficacy of local adjuvant treatment should be most evident in this group. Unfortunately, these patients cannot be reliably identified preoperatively. The efficacy of postoperative radiation therapy is being evaluated in patients with perirectal fat or lymph node involvement treated subsequent to the present series.

Conclusions

Cancer of the midrectum may be treated by ASR with a low operative mortality rate. Morbidity can be limited by the selective use of protective colostomy to minimize anastomotic complications. Proximal decompression should be used whenever there is any doubt as to the integrity of the anastomosis, and routinely in men under 65 years in whom technical difficulty may be anticipated because of a narrow heavily muscled pelvis.

ASR is applicable to a large proportion of patients with rectal cancer as determined by preoperative sigmoidoscopic measurement. More than half of the patients in this series who would otherwise have required APR had preservation of essentially normal anal continence.

The use of ASR has not resulted in a greater risk of recurrence or death from cancer. Survival rate in this series was related to site of growth and extent of spread but independent of the operation employed. Tumor invasion of perirectal fat with or without nodal involvement indicates a high likelihood of pelvic recurrence and effective adjuvant measures must be sought if the prognosis of these patients is to be improved.

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DISCUSSION

DR. MARK M. RAVITCH (Pittsburgh, Pennsylvania): You've just heard an extraordinarily clear presentation of the extraordinarily good results of a very large series of difficult patients, operated upon by a surgeon who is obviously a master of the technical problems involved. It's to the technical problems of anastomosis that I wish to direct myself.

This has occupied the time of a good many surgeons, including William Stewart Halsted, who over 20 years published a number of papers discussing what he called the bulkhead anastomotic technique: two purse strings, the bowel put together attempt to put a knife up from below to cut it. He suggested that it might be possible to put a cork borer in one end, against a cork on the other side and to cut out the double diaphragm with a cork borer.

(Slide) About 75 years later the Russians came up with this cork borer. This is from experiments we performed 11 years ago in Chicago. In essence, you have a sigmoidoscope-like instrument, the obturator goes out beyond it, two purse strings; you screw the two parts of the instruments together, squeeze the handle, and in the Russian instrument a single row of staples forms a mathematically perfect circular anastomosis at the same time that a circular knife cuts the diaphragm out.

We were unwilling, for a variety of reasons, to use that apparatus in patients at that time, although it was routinely successful in dogs, but I'd like to show you now a brief motion picture made by Dr. Felix Steichen, a new member, of the current technique with an American instrument for performing Halsted's bulkhead anastomosis for the resection of carcinomas of the rectum. [A sound film was shown.] This instrument performs an interesting anastomosis with two rows of staples, much more easily and safely than can be done by hand.

(Slide) We don't, I'm glad to say, have a postmortem specimen on a human patient, but this is from a canine patient, and you can see that there is about 1 mm or 1.5 mm of inversion and no more.

This, apparently, is going to be a useful technique for extremely low anastomoses, as well as those at conventional levels, and we're quite excited about its possibilities.

Dr. Gordon A. Donaldson (Boston, Massachusetts): I would like to commend Dr. Localio and his group for again bringing this operative procedure to our attention. First, I believe it is a sound cancer procedure for tumors of the midrectum, and second, it's an operation which always preserves the function of the anal sphincter.

At our hospital our residents have become so enamored of an operation described by Ernest Miles 70 years ago, that we have had difficulty developing a meaningful series of cases of midrectal cancers treated by an abdominosacral resection and anastomosis. Our technique differs slightly from that of Dr. Localio and is one identified with D'allaines of France, modified by Arthur Allen and described with Drs. Rodkey and Behringer in 1965.

(Slide) Our data are based on 100% follow-up—five year follow-up—of all cases operated on for cure whether or not the lymph nodes were later found to be involved. Now, it is obvious that the 81% five year cure rate in this small abdominosacral series is strictly a matter of case selection, and we believe we should be select in the choice of candidates for this operation, because of the all important matter of local pelvic recurrence following surgery. Dr. Localio brought this out in his manuscript.

If one is going to become more sophisticated in the surgical treatment of cancer of the rectum, the incidence of pelivc recurrence must not increase. In a review of all of our cases of cancer of the rectum and rectosigmoid operated upon for cure, regardless of the type of operation, we found that recurrence of disease, as identified clinically, in 30% of instances was locally in the pelvis alone—solitary pelvic recurrence. In another series of cases operated upon for cure and followed to death from disease, as many as 14% at autopsy revealed local pelvic recurrence alone. Our concern that this sphincter-preserving operation might increase this incidence of isolated pelvic recurrence was aroused by one of our patients.

(Slide) An abdominosacral procedure for cure had been done four years previously, and when this patient appeared with this recurrence at the suture line, 2 cm above the anal canal, it was necessary to perform a Miles operation. Whether this recurrence is the result of unrecognized intramural spread, or of needle implant of viable mucosal tumor cells at the time of operation, we do not know. Certainly, had she had an abdominoperineal resection in the first place, this unfortunate result would not have occurred.

This case and a similar case have led us to become more selective in our choice of candidates, and in general we have chosen patients with midrectal, adenocarcinoma tumors, usually of polypoid form and of limized size, certainly not the annular, deeply ulcerated, anaplastic lesions.

(Slide) If one is going to be this selective and particular, some may ask, "Why not fulgurate, implant radon seeds or treat such tumors with radiation?" The answer is shown in this slide. In 100 patients with tumors of the rectum 3 cm or less in diameter, subjected to a Miles resection, 12% were found to have lymph node involvement on pathological examination. In our series of abdominosacral resections, some of whom had larger tumors, 19% were found on pathological examination to have positive lymph nodes.

Since we have been more selective, we have had no further local pelvic recurrences, and in all four of the patients who later have been found to harbor disease the spread has been identified at distant sites, either in the lung, brain, spinal cord or liver. Interestingly enough, in two of these four the recurrence appeared after the five year interval; so perhaps we would do well to follow our cancers of the rectum for a longer period than five years.

I would like to ask Dr. Localio and his group two questions. First, in maintaining your recurrence rate as low as 15% after this procedure, what particular technique do you use to irrigate the anorectal segment before suture, possibly to cut down the incidence of implantation? Second, what is your program now in the treatment of these patients who have perirectal involvement of fat or lymph nodes? What type of radiation, and how much, are you using?

This paper represents a lot of hard work, and is an excellent one. I think it's for a good cause, namely, for preserving the all-important anal sphincter.

Dr. S. Arthur Localio (Closing discussion): Dr. Sabiston, I thank you for your kind words, but in reviewing the recent and old literature, we feel that the original concept of the operation was that of Kraske. We were not willing to accept things as expressed in our literature, so we had Kraske's papers and some of the other relevant European publications accurately translated. We have no question that Kraske had the notion, perhaps not in his earliest approach to cancer of the rectum, but surely later on.

In his book d'Allaines mentions the work of Kraske, Finsterer and Goetze. I would like to point out that Drs. Donaldson, Rodkey and Behringer were the first to introduce the operation to this country. Therefore, I do not believe that this operation belongs to us. We have merely modified and utilized the work of others.

Dr. Ravitch, the apparatus that you showed is one with which I have had no experience. It's an interesting one, and as you know from our discussion last night, if you make it available to me, with the various clips, I'll be happy to utilize it in the laboratory, and then, if I have the courage, perhaps in the human.

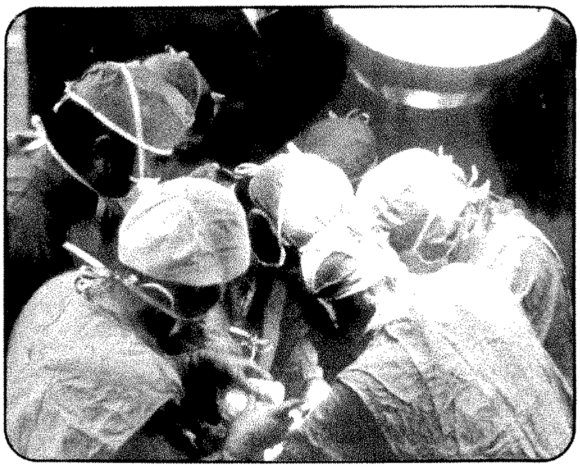
I fear that in a male, where we have the greatest difficulty with heavy levators, we might not be able to get far beyond the lesion, or perhaps not as far beyond the lesion as we do now.

I'm grateful to Dr. Donaldson for his remarks. Preoperatively, we irrigate the rectum and anus with distilled water to try to lyse tumor cells. At surgery we handle the tumor as little as possible and place a large right-angle clamp 3–4 cm (as measured with a ruler) below the tumor. Perhaps, that's been responsible for keeping the recurrence rates reasonable.

We had one patient not unlike yours in which we had to go back and perform an abdominoperineal resection. We are troubled by the inadequate results in all cancers of the rectum in the Dukes' C patient and in the Dukes' B patient with infiltration of the perirectal fat. About two years ago we commenced treating these patients postoperatively with 4500 rads after they had overcome the effects of their operative procedure. It's too early to assess the value of this therapy.

We have hesitated to treat patients preoperatively for it necessitates unnecessary radiation of Dukes' A and some Dukes' B patients. I know that Dr. Silen (and I'm delighted that Dr. Silen is doing this operation) is radiating his patients both pre- and postoperatively. I suspect that his data will be terribly important.

The O.R.



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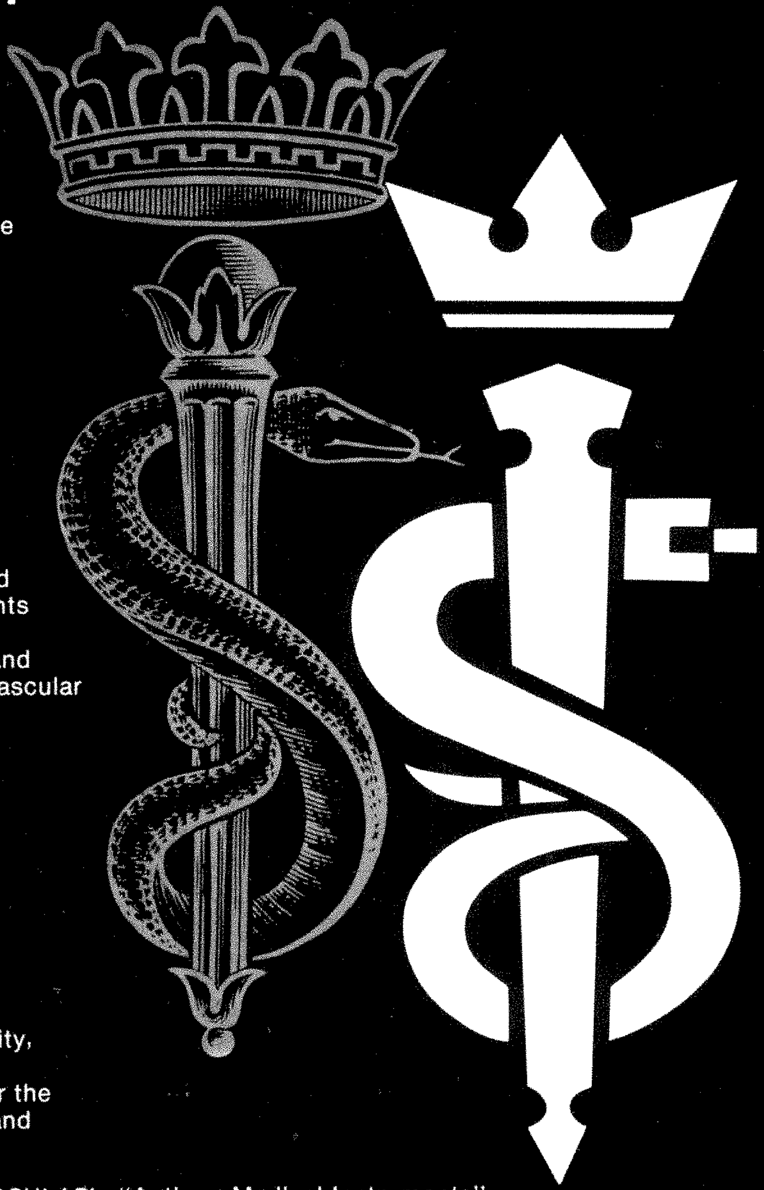

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Use of CEA as an Indicator of Early Recurrence and as a Guide to a Selected Second-look Procedure in Patients with Colorectal Cancer

HAROLD J. WANEBO, M.D.,* MAUS STEARNS, M.D.,† MORTON K. SCHWARTZ, PH.D.

The usefulness of the CEA as an indicator of recurrence and a guide to selected second-look surgery was evaluated from a retrospective analysis of 358 patients with colorectal cancer and from a prospective experience with 16 patients all of whom had been admitted for second-look surgery because of postoperative elevations of CEA only. Our previous experience had shown that after curative resection the CEA usually returned to normal levels (less than 5 ng/ml) within one month, but became elevated at time of clinically obvious recurrence being very high in patients with liver metastases, but only moderately elevated or normal in patients with local recurrence. All 16 patients had previously had curative resection of colorectal cancer; 13 in the rectum or rectosigmoid and three in the right colon. There were 13 Dukes' C and three Dukes' B cancers. All had been followed clinically and by CEA testing at three monthly intervals and were considered free of disease (NED) at time of CEA elevation.

The median disease free interval was 13 months (range 4–57 months) and the median CEA prompting admission for second-look operation was 21 ng/ml (range 10–56 ng/ml). The sites of recurrence were liver in six, lung in two and localized disease in six. Two patients had negative exploration for recurrence and were found to have cholelithiasis only (one of these later died of metastases). Resection for cure was done in seven and palliative resection or biopsy only was done in nine patients. At this time, four patients are NED (12–37 months), five are living with disease (10–16 months) and seven have died of disease (2–12 months). The CEA test provides a method of early detection of recurrence and may permit surgical retrieval in selected patients and earlier initiation of palliation in other patients. The long-term effects in patient salvage remain to be defined.

THE SECOND-LOOK PROCEDURE to demonstrate recurrence in colorectal cancer was first popularized by Wangensteen in 1951.[44] Although this follow-up approach of patients who were at high risk for recurrence was theoretically sound, these operations never gained wide acceptance. Many were performed too late to materially affect the patient's clinical course, and the considerable morbidity and even mortality accompanying the procedure precluded widespread adoption. The development of the carcinoembryonic antigen assay with its potential for detecting subclinical recurrence has revised interest in a second-look surgery as selectively indicated by serial rises in the CEA.[25]

Although the carcinoembryonic antigen is not specific for colorectal or other gastrointestinal cancers as once thought,[9,10] it is uniquely useful as a tumor-associated antigen to assist in the clinical evaluation of patients with colorectal cancer.[12–15,21–23] It correlates well with stage of disease[3] and prognosis,[14,21] and appears useful in many cases in the early detection of recurrent tumor.[14,22,23,27] Martin et al., have recently documented the reliability of serial CEA determinations as an early indicator of recurrent gastrointestinal cancer and a guide to the performance of second-look surgery.[25] They defined a CEA nomogram based on analysis of intra-assay and inter-assay variability which could be used to compare serial CEA changes to determine whether a change was significant. If there was a significant increase beyond the 95% confidence limits for that observation, the study was repeated. If there was again a significant increase then a second-look procedure was considered. Martin et al. found that a statistically significant rise above baseline levels proved to be a correct indicator of tumor in 88% of the patients whom they explored for recurrence. In this series, other diagnostic tests were normal. Of 22 patients with recurrence, 16 (73%) had distant metastases and six (27%) had localized tumors.[25]

We report here our experience with CEA level as an

Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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indicator of recurrence and a guide to a selected second-look surgery, from a retrospective analysis of 358 patients with colorectal cancer and from a prospective experience with 16 patients, all of whom had been admitted for second-look surgery because of postoperative elevations of CEA only.

Materials and Methods

CEA Assay

From 1970 to 1976, preoperative CEA elevations were performed at Hoffman La Roche (Nutley, N.J.) by the Hansen method,[12] and at Memorial Sloan Kettering Cancer Center (New York, N.Y.). From January 1975, serial postoperative assays were performed at MSKCC. Results of tests performed in both laboratories were in close agreement. The blood samples were drawn before operation, and three to seven days, one week and two weeks after operation, and then two to four month intervals for two years, and at four to six month intervals up to 60 months in selected patients. CEA levels of 0–2.5 ng/ml were considered normal whereas levels of 2.6–5.0 ng/ml were considered borderline, and levels higher than 5 ng/ml abnormal.

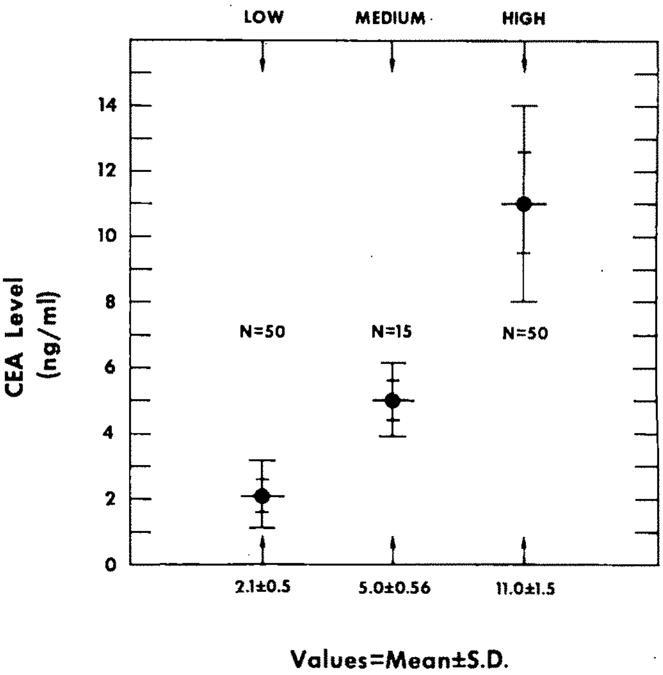

FIG. 1. The prevision of daily CEA assays as performed on standardized aliquots of plasma containing low, intermediate and high amounts of CEA. The coefficient of variance was 24%, 11% and 14% respectively. The range within the 95% confidence level for the three basic concentrations was *low*, (1.1–3.1 ng/ml), *medium* (2.9–6.1 ng/ml) and *high* (8–14 ng/ml).

Clinical Material

The initial studies included 358 patient with colorectal cancer and 47 patients with benign colonic lesions treated by the Rectum and Colon Service at MSKCC from 1970 to 1975. Two hundred three patients had primary operable cancer, and 155 patients had recurrent or metastatic cancer. The patients had physical examinations and sigmoidoscopy every two to four months and barium enema, chest film, intravenous pyelogram and liver function tests every 6–12 months. Sequential tests were performed in 153 patients with resectable primary cancer. The precision of the daily CEA assays is shown in Figure 1. The precision data was developed by daily assaying of a pool of control blood containing normal CEA levels and blood to which purified CEA was added, to yield CEA values in the intermediate or high range. The mean and standard deviations for the three ranges of CEA levels were as follows: Low—2.1 ± .05 ng/ml; medium—5.0 ± 0.56 ng/ml; high—11.0 ± 1.5 ng/ml. The coefficient of variance ranged from 24% for low values to 14% for high values. If we use 2 SD (95%) as the outer confidence limits, the range of those values would be: low—1.1–1.3 ng/ml; medium—3.9–6.1 ng/ml; and high—8–14 ng/ml. Thus, serial changes in individual patients outside of these ranges should prompt a repeat of the assay. If the CEA is confirmed as rising, then the study would ideally be repeated in one month and if the rise is confirmed again, the patient would be considered for admission for evaluation and possible second-look surgery. In this series, a nomogram was not used but, rather, CEA changes considered significant by the clinician were used as the indication for repeated testing and admission for evaluation for a second-look surgery. In general such CEA levels had risen above 10 ng/ml.

Results

Reaction of CEA to Stage of Disease

CEA levels correlated well with stage of disease.[43] The proportion of patients with abnormal CEA levels (greater than 5 ng/ml) was 4% in Dukes' A, 26% in Dukes' B, 44% in Dukes' C and 65% in Dukes' D (most of whom had liver metastases at the time of primary operation), and 72% in patients with recurrent or metastatic cancer ($p < .05$). The preoperative CEA also correlated with prognosis.[43] Patients with CEA greater than 5 ng/ml (either Dukes' B or C) had significantly increased recurrence rates in comparison to patients with values less than 5 ng/ml.

In 155 patients with advanced colorectal cancer, those with liver metastases had the highest frequency of elevated CEA levels, whereas those with local recurrence had a lower frequency of elevated levels.[43] Ninety-two per cent (48/52) of the patients with liver metastases had CEA levels higher than 5 ng/ml, compared to 50% (23/46) of patients with local recurrence. In those with lung and bone metastases, all 12 patients had elevated values. The highest values *per se* were found in patients with liver metastases. Forty of 52 (77%) such patients had CEA greater than 20 ng/ml versus 10 of 46 (22%) patients with local recurrence ($p < 0.001$).[43]

Changes in CEA Levels After Tumor Resection

The changes in CEA after surgery depended on the initial preoperative levels and the stage of disease (Fig. 2). Patients with normal (<2.5 ng/ml) or borderline CEA levels (2.5–5.0 ng/ml) usually had normal levels two weeks after operation. Patients with normal preoperative values showed only minimal changes after operation and generally remained normal during the first two to four weeks after operation. Of 52 patients with Dukes' A lesions who had preoperative CEA lower than 5 ng/ml, only three patients' CEA levels failed to return to levels lower than 2.5 ng/ml. Three patients with CEA higher than 5.0 ng/ml retained elevated values postoperatively. Of 40 patients with Dukes' B lesions, who had preoperative values lower than 2.5 ng/ml, 34 patients maintained those values, but six patients had an increase in CEA to the 2.6–6.1 ng/ml range. Overall, of 47 patients who had preoperative values lower than 5.0 ng/ml, 40 had return to normal values (lower than 2.5 ng/ml) in the period of two to four weeks after operation. Of 20 patients with preoperative CEA greater than 5 ng/ml, one-half had normal values (<2.5 ng/ml) two weeks postoperatively. In patients with Dukes' C lesions, only one of 19 with preoperative CEA lower than 2.5 ng/ml had an elevated CEA level postoperatively. However, among the patients with slightly elevated CEA levels in the 2.6–5.0 ng/ml preoperative range, six of 14 retained higher values than normal (2.6–4.6 ng/ml). Among the patients with preoperative CEA higher than 5.0 ng/ml, 12 of 16 had abnormal values (higher than 2.5 ng/ml) postoperatively and in eight patients, the CEA level remained above 5 ng/ml. There was a high recurrence rate in patients whose CEA level remained above 5.0 ng/ml postoperatively. Four of 6 patients (67%) with Dukes' B lesions and all of 8 patients (100%) with Dukes' C lesions, whose CEA level remained above 5.0 ng/ml after resection, developed recurrence.

Sequential Changes in CEA After Curative Resection—Correlation with Recurrence

A group of 55 patients with Dukes' B and 64 patients with Dukes' C lesions have had sequential follow-up of CEA levels over a 12–58 month period after curative resection. The patterns of changes in CEA levels which accompanied recurrence were distinctively particular to the type and site of recurrence.

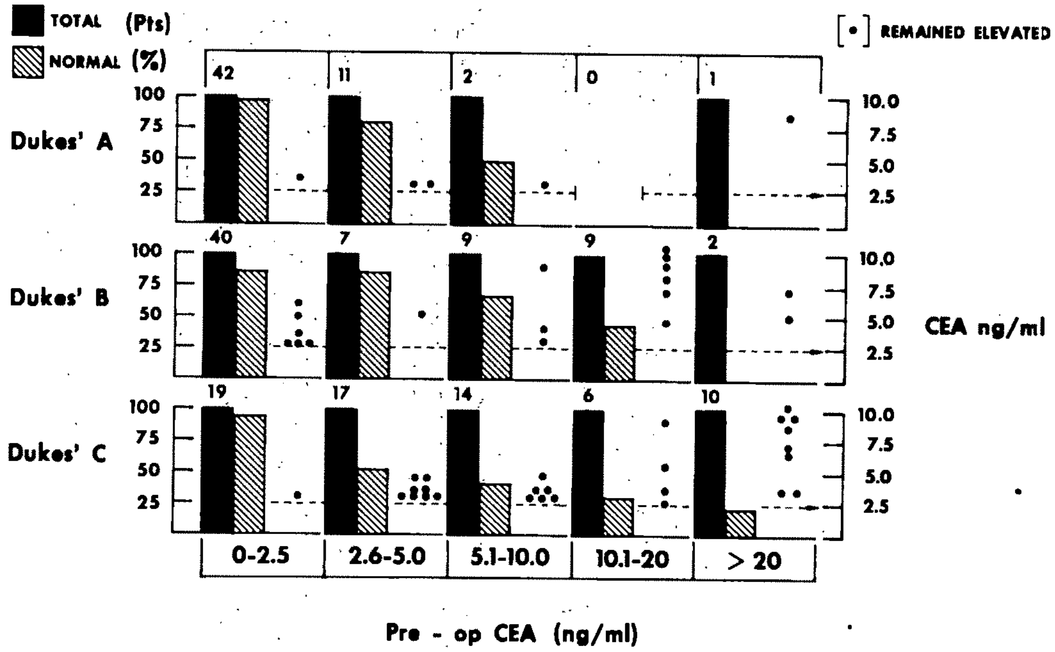

FIG. 2. The frequency of normalization of CEA levels two weeks after curative resection varied according to the preoperative CEA and the stage of disease. In general, patients with normal (less than 2.5 ng/ml) or borderline (2.5–5.0 ng/ml) preoperative values had normal postoperative levels in comparison to those presenting with high preoperative (greater than 5 ng/ml) levels who frequently maintained abnormal levels after operation.

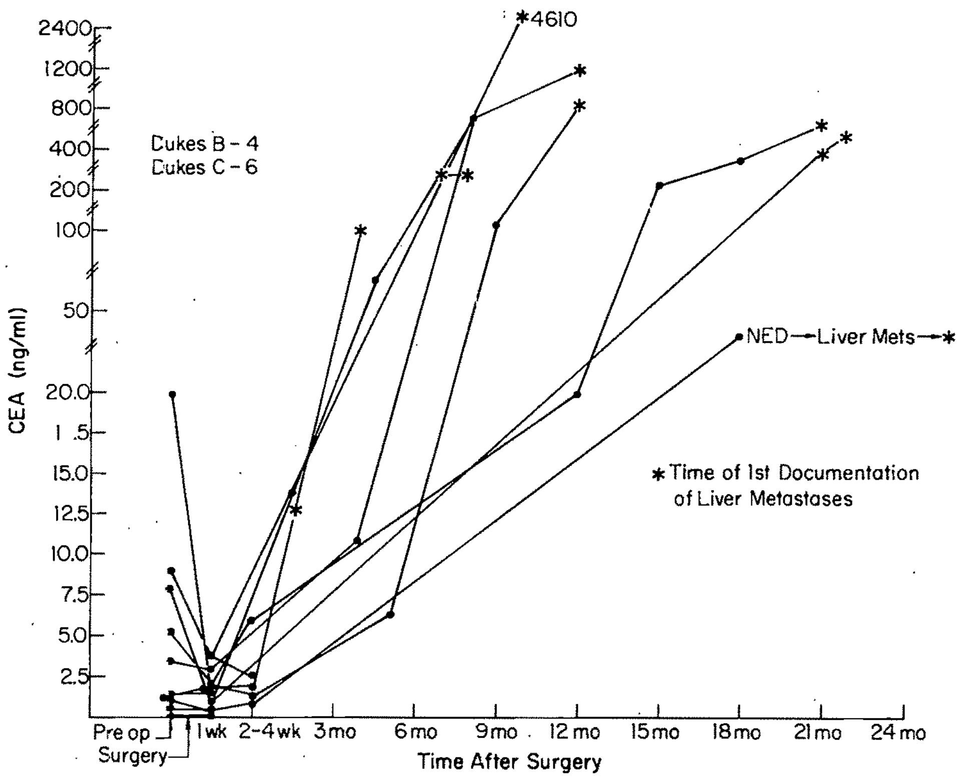

FIG. 3. In ten patients who developed liver metastases, four showed a rapid fall in CEA during the immediate post-operative period, but then all showed a rapid rise in CEA prior to clinical evidence of liver metastases.

CEA levels often rose rapidly prior to clinical or biochemical evidence of liver metastases as shown in the illustration of ten patients who developed liver metastases after curative resection. All ten developed a rapid rise in CEA prior to clinical evidence of recurrence in the liver (Fig. 3). In contrast, in patients with local recurrence, the CEA level rose more slowly and was frequently within normal limits at time of clinical recurrence. This is shown in this series of eight patients of whom seven had normal CEA levels, at the time of local recurrence (Fig. 4). The pattern of CEA elevation varied more in patients who developed intraabdominal, lung or bone metastases. In general, the highest absolute CEA levels occurred in patients with liver metastases.

Prospective Experience with CEA as an Indicator For Second-look Surgery

In 16 patients the CEA elevation was the major reason for admission for second-look surgery (Table 2). Thirteen had been operated for Dukes' C and three for Dukes' B cancer. The median disease-free interval was nine months (4–57 months) and the median

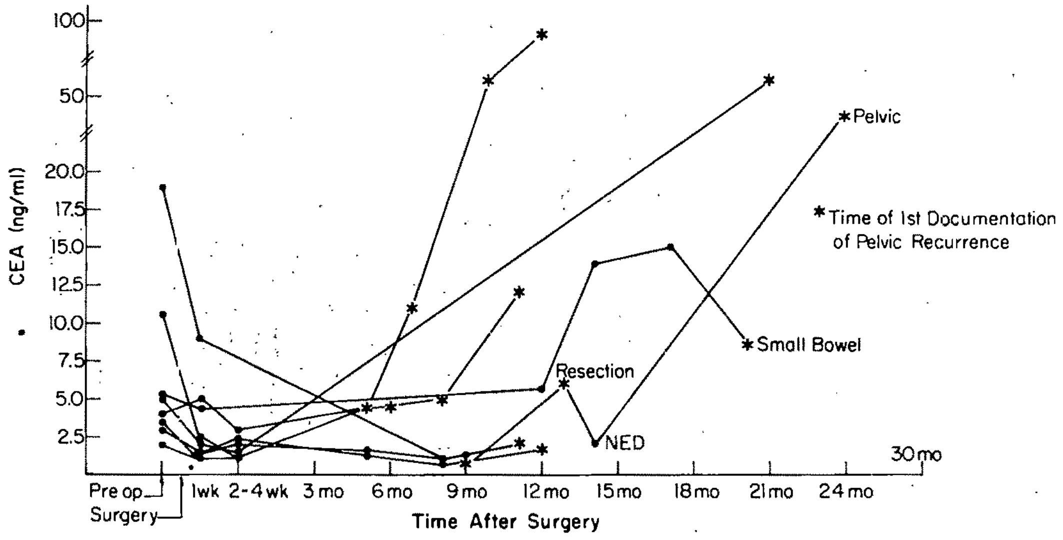

FIG. 4. In eight patients who developed local recurrence only, seven showed clinical evidence of pelvic recurrence prior to CEA elevation and in only one did a rising CEA precede clinical recognition of recurrence.

CEA prompting second-look surgery was 26 ng/ml (range 10–57 ng/ml). The site of recurrence was liver in six patients, local pelvic disease in six and pulmonary metastases in two patients. Two patients had "false-positive" elevations of CEA and had a negative laparotomy. Curative resection was possible in seven patients and a palliative resection or biopsy only was done in six patients. One patient was admitted for second-look surgery and was found to have nodules in lung and liver which were biopsied only.

TABLE 1. *Correlation of CEA with Site of Recurrent Colorectal Cancer*

Major Metastatic Site	Pts.	<5 ng/ml	5.1–20 ng/ml	>20 ng/ml
Liver	52	8%	16%	76%
Lung-Bone	12	0	42%	58%
Abdomen-Viscera	45	36%	31%	33%
Local-Pelvis	46	50%	28%	22%
Total	155	28%	26%	46%

Modified with permission from Wanebo, H. J., Rao, B., Pinsky, C. M., et al.: The Use of the Preoperative Carcinoembryonic Antigen Level as a Prognostic Indicator to Complement Pathologic Staging, N. Engl. J. Med. Aug. 28, 1978.

Results of Second-look Surgery (Table 3)

Of the six patients in whom the recurrence was limited to the liver (patients 1–6), two patients had disease localized to a single lobe, and were amenable to resection (left hepatic lobectomy in one and segmental resection of left lobe in one). One of these patients died of disease eight months later, whereas the other patients had no evidence of disease (NED) 15 months after second-look surgery (Fig. 5). Of the remaining four patients, two were still living with disease at 10 and 15 months and two were dead of disease at seven and nine months.

There were six patients who were found to have recurrent disease localized to the pelvis or abdomen (patients 7–12). Four were resected for cure and two had palliative procedures. One patient (K.C.) had two second-look procedures (Fig. 6). The initial procedure was done nine months after a primary right hemicolectomy for Dukes' B cancer, at which time the patient was found to have ovarian metastases, which were resected. Her CEA, which had risen to 38 ng/ml, returned to 3.6 ng/ml and she remained well until 31 months later when a routine chest film showed a nodule in the right upper lobe (CEA was normal then). At thoracotomy, metastatic adenocarcinoma was demonstrated and a lobectomy was performed. She was well six months later, 37 months after the initial second-look procedure. In the six patients with local abdominal recurrence, two patients were alive and well 12 and 37 months after the second-look procedure, two were living with disease at 12 and 16 months and two died of disease at two and 12 months (Table 3).

There were two patients with metastases to lung. One patient admitted for second-look surgery because of a rising CEA level was found to have multiple pulmonary nodules and a positive liver scan. A percutaneous biopsy confirmed metastatic colon carcinoma and chemotherapy only was initiated. A second patient in the CEA study was found to have a solitary lesion in the lung and underwent a lobectomy for metastatic colon cancer. At the time of lobectomy, the surgeon was suspicious of a possible mass in the liver which could be palpated through the diaphragm. Postoperatively the patient did well but now has developed intra-abdominal metastases and is living with disease 12 months after the second-look procedure.

Two patients had false CEA elevations and had negative second-look operations. In one, (H.F.), who had previously had resection of a recurrence involving the right ureter and colon, a rise in CEA to 12 ng/ml prompted a second-look operation (Fig. 7). Detailed exploratory laparotomy with multiple biopsies of liver and paracolic gutter were done. No tumor was found, but cholelithiasis was demonstrated and a cholecystectomy performed. The patient continued to do well 22 months after this surgery, in spite of CEA fluctuations between 5–18 ng/ml. The other patient (A.S.), had been followed after resection of an extensive carcinoma which involved the transverse colon, pancreas, and stomach and developed a CEA of 46 ng/ml 57 months later (Fig. 8). A second-look operation with multiple biopsies was done, but no tumor was found. A cholecystectomy was done for gallstones, and the patient was discharged and was considered to be NED during his subsequent follow-up. Eight months later he had acute onset of paraplegia and died one week later of multiple metastases to spine and other sites.

We have continued to obtain serial CEA measure-

TABLE 2. *CEA—Use as Indicator for "Second-look Surgery" in Colorectal Cancer*

Site	Pts.	Curative Resection	Palliative Resection or Biopsy
Liver	6	2	4
Local-Pelvis	6	4	2
Lung	1 (1)*	1	
Lung-Liver	1		none
False-Positive	2		2 (cholecystectomy & mult. biopsies No cancer)
Total	16	7	9

* (1) patient had resect. of local & lung mets. separately.

TABLE 3. *Selected Second-look Surgery in Colorectal Cancer*

Patient	Primary Surgery-Path	Disease Free Interval	Postop Change in CEA ng/ml	Site of Recurrence	Treatment	Therapy Post "Second Look"	Follow-up CEA ng/ml	Disease Status After Second-Look Surgery
1. 44 y.o. F J.W.	Subtotal coletomy 4/16/76 Dukes' C	9 mo.	Pre op 1–26	5 cm met. (L) lobe of liver	Resection of (L) lobe 1/26/77	MeCCNU + 5 FU	N.D.	DOD 8 mo.
2. 55 y.o. F L.U.	Ant. res. BSO 2/14/73 Dukes' C	43 mo.	2.6–16	6 cm. met. (L) lobe of liver	Wedge resection of liver (L) 9/3/76	MeCCNU + 5 FU	0.3–3	NED 15 mo.
3. 67 y.o. M V.M.	Ant. res. 5/18/73 Dukes' B	41 mo.	3.4–45	Large mass medial (R) lobe of liver	Biopsy only 10/18/76	M.O.F. Chemo.	123–250	1/78 LWD–15 mo.
4. 58 y.o. M S.C.	(L) hemicolectomy 9/18/75 Dukes' C	13 mo.	1.3–47	Large lesion (R) lobe of liver	Biopsy 12/76 later cannulation of portal vein	Infusional chemo. Phase I. chemo.	190–1180	DOD 7 mo.
5. 52 y.o. M J.D.	Sigmoid res. Exc. of met. in (R) lobe 11/3/75 Dukes' C	9 mo.	2.0–24	Multiple liver metastases	Biopsy cannulation of hepatic A & hepatic V 8/19/76	Infusional 5 FU + Act D	52–55	DOD 9 mo.
6. 50 y.o. F H.W.	Ant. res. BSO Dukes' B, Gr II Liver met–(L) 3 × 7 nodule res. 8/11/76	9 mo.	2.4–49	Liver 5 nodules (R) 2 nodules (L)	Biopsy only 5/11/77	MeCCNU + 5 FU	104–178	LWD 10 mo.
7. 54 y.o. F S.G.	1969–APR Dukes' C 1973–Sacral recurrence radiated 11/10/75–Resect. of sacral rec.	15 mo.	1.3–10	Nodule in pelvic floor	3/15/76 Excised pelvic nodule	MeCCNU + 5 FU	7–18	? NED 12 mo.
8. 47 y.o. F K.G.	5/2/74–(R) hemicolectomy Dukes' B	9 mo.	–38	Mets. to (L) ovary	2/6/75 (L) salpingo- oophorectomy	5 FU	3.6–4.8	Nodule RUL 9/15/77 lobectomy–adenoca. NED 3/78 37 mo.
9. 35 y.o. F C.M.	7/9/75–Ant. res. BSO, TAH Preop 4000r Dukes' C	9 mo.	14–57	Recurrence (L) ureter and sigmoid	4/28/76 Res. sigmoid & ureter Hartmann	MeCCNU + 5 FU	N.D.	*Pelvic recur.* LWD–12/77 16 mo.
10. 67 y.o. M H.H.	12/19/75 Low ant. res. Dukes' C	13 mo.	1.9–12	Nodule (R) lung	2/1/77 Res. lung met.	MeCCNU + 5 FU	50–168	LWD 2/78 12 mo.
11. 50 y.o. F E.L.	5/3/73 Sigmoid colectomy Dukes' C	22 mo.	2–50	Omental mass, para-aortic LN + "non- functioning (L) kidney	3/17/75 Res. omental mass Marked LN with clip	Postop radiation	16–2–38	Good palliation, "Pelvic recurrence" ? DOD 8/77 12 mo.
12. 68 y.o. F E.H.	3/5/76 Res. sigmoid & (L) ureter Dukes' C	9 mo.	6.8–18	? liver mets. S. bowel fistula pelvic abscess	2/18/77 Lap. res. fistula	Radiation	N.D.	Rapidly progressing DOD 2 mo.
13. 68 y.o. F M.P.	6/2/76 Large sigmoid ca. res. with BSO Dukes' C	4 mo.	14–48	Admitted for Second-look, had lung nodules & + liver scan	No surgery Percutaneous biopsies	MeCCNU, Oncovin 5 FU + Strep	80–580	Slow progression DOD 13 mo.
14. 49 y.o. F H.R.	12/22/76 Rectal ca with mets. to ovaries. Ant. res. + BSO Dukes' C	7 mo.	–13	Multiple liver nodules & carcinomatosis	Biopsy only	Phase I chemo.	–134	Slow progression LWD 4 mo.
15. 49 y.o. M A.S.	4/73 Res. trans. colon, stomach, distal pancreas spleen, kidney Dukes' C	57 mo.	–46	No tumor found cirrhosis, cholelithiasis cholecystitis	Liver biopsy cholecystectomy, Neg. lap for tumor	None	–93	Acute paraplegia spine mets. DOD 1/14/78 8 mo.
16. 61 y.o. M H.F.	1972–(R) hemicolectomy, Dukes' C cecum 2/75–(R) hydronephrosis, omental implant res.	30 mo.	–11.8	No tumor found gallstones, diverticulosis scar tissue	Lap-biopsy of liver, scar tissue, cholecystectomy	MeCCNU + 5 FU	5–18	NED 22 mo.

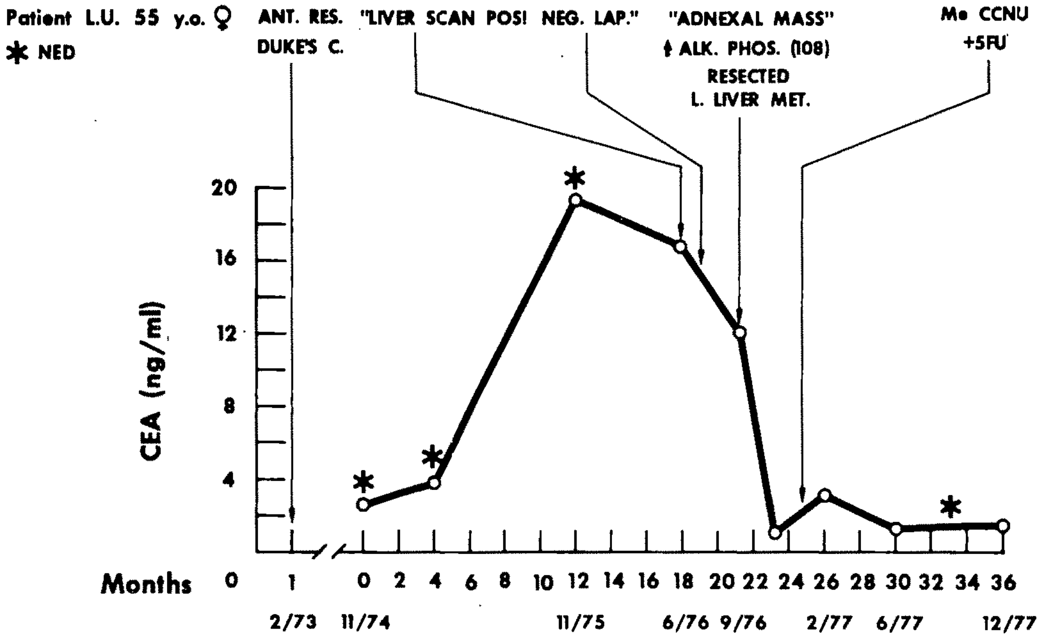

FIG. 5. The above patient (L.U.) developed a rising CEA after curative resection of a Dukes' C rectal cancer and had a laparotomy which was "negative for tumor" 18 months postoperatively. Subsequently an adnexal mass was palpated. Re-exploration six months later showed a 6 cm metastasis to the left lobe of liver (and no pelvic disease). Following a large wedge resection she remains NED 15 months later.

ments after second-look surgery. If the patient has a localized recurrence that can be resected, the CEA is useful for long-term observation of the "disease-free stage." If it again is elevated, a third-look procedure may be needed in selected patients. In patients who were found to have unresectable disease, the CEA measurements have been useful in long-term assessment of their response to radiation and chemotherapy. An example is patient E.L. who underwent a palliative resection of an omental mass and was given postoperative radiation to para-aortic lymph nodes. She responded well clinically, and her CEA returned to normal, but rose again with exacerbation of recurrent disease prompting careful re-examination and documentation. Chemotherapy with 5 Fluorouracil and Methyl CCNU was started but she expired 20 months later which was 30 months after her initial second-look operation (Fig. 9).

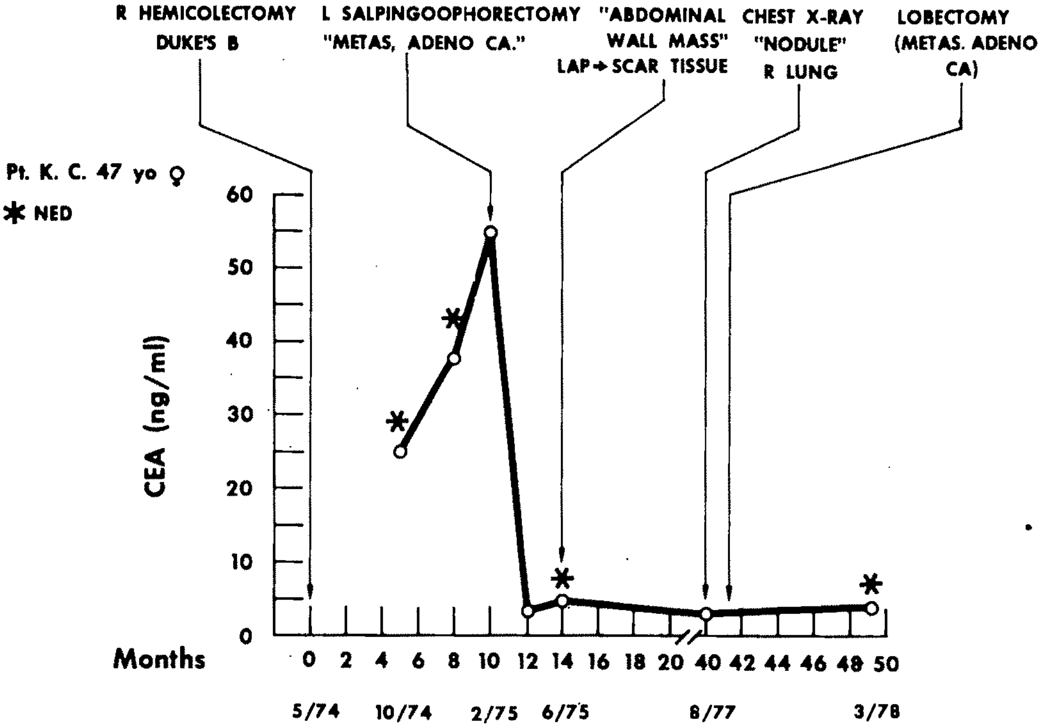

FIG. 6. This patient (K.C.) had two second-look procedures, one at ten months after initial curative resection and the second at 40 months. The patient is currently NED.

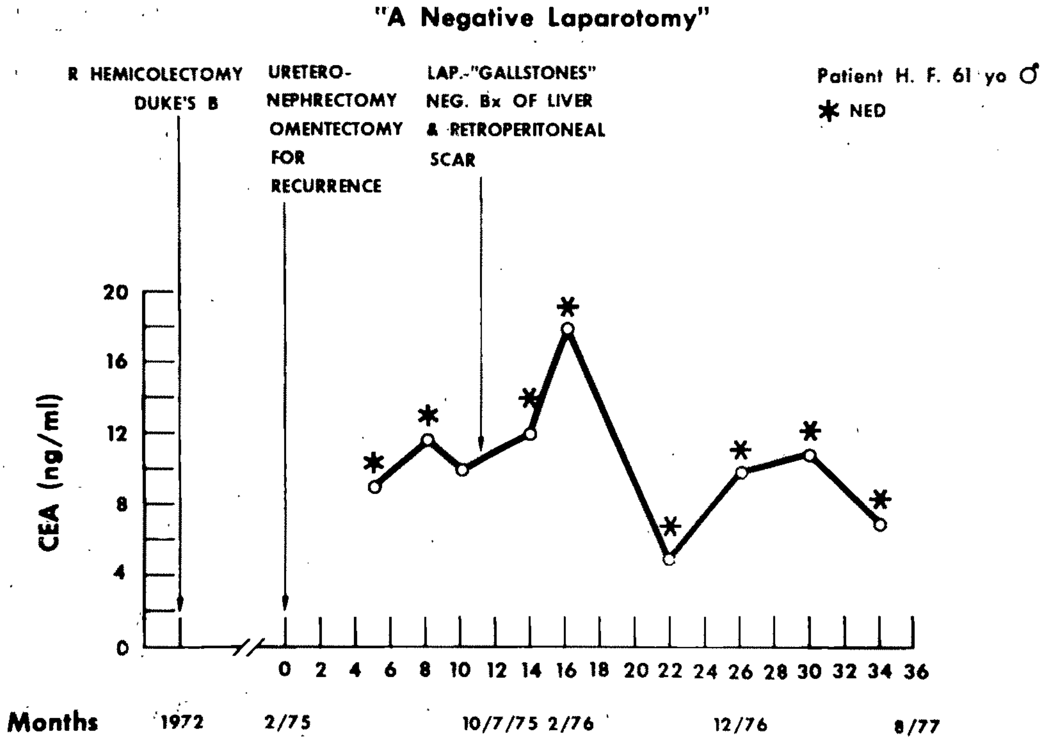

FIG. 7. This patient (H.F.) had previously had a Dukes' B cancer and developed recurrence which was resected. A rising CEA (in absence of smoking) prompted a second-look procedure but no tumor was found and a cholecystectomy was done for stones. He was still NED 22 months later in spite of continued CEA elevations.

Discussion

In our overall study of CEA in patients with colorectal cancer, we have observed the following. 1) CEA levels are correlated with stage of disease. 2) CEA levels are elevated in three-fourths of the patients with recurrent or advanced disease. They are highest in patients with liver metastases or disseminated disease, but are frequently normal or only slightly elevated in patients with local or pelvic recurrence. 3)

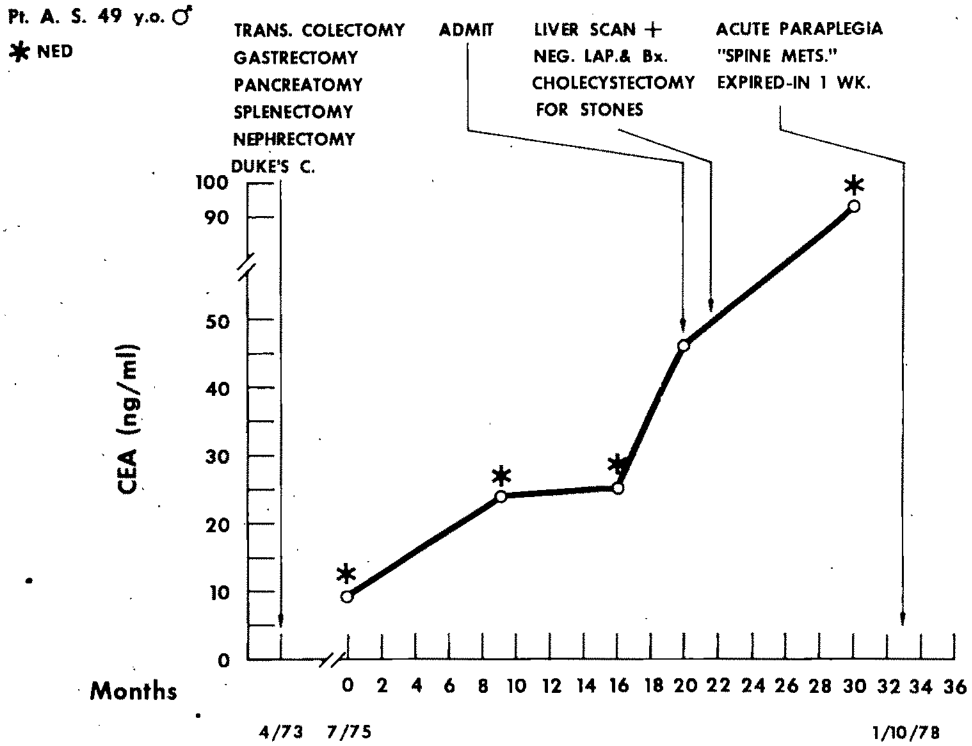

FIG. 8. An exploratory laparotomy was done for a rising CEA (46 ng/ml). Cholelithiasis was demonstrated, but multiple biopsies were negative for tumor. The patient was considered to be NED but eight months later died from rapidly progressing metastases.

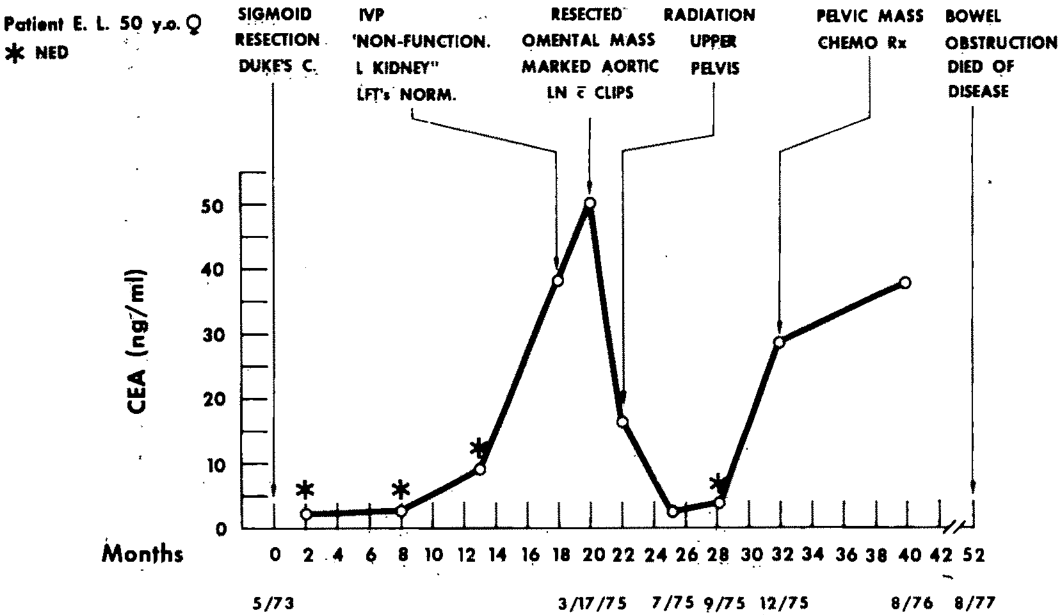

FIG. 9. There is continued usefulness of serial CEA studies after "palliative" second-look surgery. This patient responded clinically and her CEA levels decreased in response to radiation. The development of recurrence of her tumor coincided with rapidly increasing CEA levels.

An elevated preoperative CEA level is associated with worsened prognosis in patients who have curative resections. 4) Postoperative sequential CEA measurements are a useful adjunct in clinical follow-up of patients after curative resection, and may provide an earlier indication of recurrence than can be determined clinically.[43] The test is most useful in patients who develop liver metastases, but is of more limited use in patients who develop local recurrence, in which case it must be complemented by careful clinical and laboratory assessment. Additional tests to detect pelvic or local abdominal recurrence, should include periodic hemoccult slide tests, endoscopy, intravenous pyelograms, barium studies and sonogram or computerized axial tomography (CAT scan) if available.

Our initial experience with the use of serial changes in CEA as an indicator for selected second-look procedure suggests potential benefit for patients who are at a high risk for recurrence. A curative resection was possible in seven patients and a palliative resection or biopsy only was done in six. Short-term salvage was provided in only four patients, however (one of these actually had a negative second-look procedure in spite of CEA elevations). There were five patients living with disease, a mean of 12 months after second-look surgery (10–16 months). All were maintained on chemotherapy. Seven patients died of disease at a mean of seven months (2–12 mo.) after second-look surgery. There were two negative explorations for apparent false-positive CEA elevations. In one of these cases, however, the patient developed and died from metastatic colon cancer eight months later.

The initial second-look procedures, as fostered by Wangensteen, were updated in the report of Gunderson and Sosin[11] and afford a good comparison with our own small series. Fifty-two of 75 patients who had second-look surgery after abdominal perineal resection for cure of rectal and rectosigmoid cancer were found to have tumor at that time. Only four patients were converted to a disease-free state by this surgery. This is lower than our initial result of seven of 16 patients being rendered free of tumor, although only four of these remained disease free at this time. Our method of selecting patients for second-look surgery is less exacting than that reported by Martin et al.[25] In their series, the use of a nomogram and the stimultaneous study of frozen serial samples permitted a more sensitive early detection system. Indeed, selected patients in this study were explored on the basis of sequential rises in CEA which were still in the normal range. They recommended obtaining CEA studies every month during the first year, every two months

TABLE 4. *CEA—Use as Indicator for "Second-look Surgery" in Colorectal Cancer*

Resection of Recurrence	Survival Results (months)		
	NED	LWD	DOD
Liver (6 pts)	15	13,10	7,8,9
Local-Abdominal (6 pts)	12,37	16	2,4,12
Lung (2 pts)		12,13	
Other (2 pts)			
Negative laparotomy	22		8
Total Patients	4	5	7
	(12–37 mo.)	(12–16 mo.)	(2–12 mo.)

in the second and third years and every three months in the fourth and fifth years. This would require 32 tests (at $30/test, this would cost $960). The cost-benefit ratio may not be appropriate for patients with low-risk lesions but may well be worth the effort in high-risk patients. The sites of recurrence in Dukes' B and C patients as recorded by Gunderson and Sosin were localized to the pelvis only in 48%, pelvis and distant metastases in 92% and distant metastases in 7.7% only.[11] The CEA changes with local pelvic recurrence are often small and may fail to prompt clinical recognition. In the series by Moertel et al.[30] only 25% of patients with local recurrence had CEA elevations greater than 5 ng/ml (In our series it was 50%). Perhaps by maintaining baseline CEA samples in high-risk patients, one might select patients with local recurrence at a far earlier time in their disease process.

With the knowledge of the risk factor correlations of CEA levels in patients with operable colorectal cancer, we can select a group of patients in whom this close scrutiny is indicated and, conversely, exclude those in whom the likelihood of recurrence or CEA changes is small.[2,4,11,42] High-risk patients would include patients with Dukes' B (B_1 or B_2) and C_1 or C_2 lesions and the occasional patient with Dukes' D cancer, who have had all gross disease resected,[2,4,42] patients with an elevated preoperative CEA (greater than 5 ng/ml) and especially those patients with persistent CEA elevations after surgery.[43] The latter group is at extremely high risk for recurrence, as 20 of 21 patients (86%) with Dukes' B and C lesions whose CEA failed to return to normal (less than 5.0 ng/ml) after surgery developed recurrence.

Although Moertel et al.[30] have stated that the CEA is not a sensitive test for early recurrence of colorectal cancer, this would appear to be hypercritical of the overall usefulness of the assay, though it may frequently apply in patients with local recurrence alone. Our data generally supports this aspect of his observation, as one-half of our patients with local recurrence had normal CEA values. In the present series, however, there were changes in CEA levels in six patients with local recurrence which prompted second-look operations and four of these had an effort at curative resection. Certainly in patients with early liver metastases, the changes in CEA are more dramatic (almost all were elevated above 5 ng/ml) and should prompt earlier recognition of recurrence. In patients with a solitary metastasis a resection for cure is feasible and in those patients with nonresectable metastases earlier chemotherapy by infusion or by systemic routes can be initiated.

There is not unanimity of opinion regarding the benefits of serial CEA determinations in detecting early recurrence. The opinions range from "not useful"[30] to "very optimistic."[25] Several studies have evaluated serial CEA determinations after resection of large bowel cancer with curative intent. Sugarbaker et al. studied monthly CEA levels in 32 patients, of whom 12 subsequently developed recurrence.[36] A rising CEA was the first evidence of recurrence in only four, and all four had distant metastases (supraclavicular nodes, retroperitoneal nodes and liver). Mach et al., in a follow-up of 17 patients after resection of all disease, demonstrated late CEA rises in nine patients, of whom three showed recurrence (only one of these had localized recurrence).[22] Mackay et al., observed 220 patients after curative resection of colorectal cancer.[23] Seventeen patients showed a CEA rise above normal but had no clinical evidence of disease (nor were they explored). Among 53 patients with confirmed recurrent or metastatic disease, 36 showed a previous or simultaneous rise in CEA level and 17 showed no change. Six patients had local recurrence only and two of these had shown a rising CEA level. Other authors have been more sanguine about the use of the CEA in detection of recurrence after curative resection. In Herrera's study of 23 patients who developed clinically evident recurrence, 20 had an elevation of CEA at the time of clinically apparent recurrence and in 14 patients the CEA was elevated a mean of five and one-half months prior to clinically evident recurrence.[14] Neville and Cooper have reported a collected series of 82 patients who developed recurrence in whom sequential CEA tests were monitored.[31] In 63 patients the CEA elevation coincided with recurrence, whereas in 19 patients the CEA remained normal at the time of recurrence. These authors did find that CEA elevations occurred prior to clinically detectable recurrence in 37 patients. CEA elevations occurred as the first sign of recurrence in over one-half of the patients. There were false-negative CEA values, however, in about one-fourth of the patients. In our own series, CEA elevations were almost universal in patients with liver metastases (92%), but were much less frequent in patients with pelvic recurrence (50%). False-positive elevations of CEA may also occur in patients who are being followed after curative resection of colorectal cancer. In the Roswell Park series, four of 23 patients who developed CEA elevations had no evidence of recurrence.[14] These patients had at least two sequential elevations of CEA and subsequently had return of these values to normal.

Martin et al. have been the most successful in the use of sequential CEA determinations to indicate a selected second-look procedure.[25] They established a CEA nomogram for measuring the observed CEA level against the 95% confidence limit for that observation in order to identify a statistically significant increase. A statistically significant rise above the baseline nomogram values was a correct indicator of tumor recurrence in a retrospective analysis in 22 of 25 patients (88%) who underwent second-look intraabdominal procedures (22 colorectal cancer, two gastric and one pancreatic cancer). In each case, other laboratory studies were normal. Of 22 patients with proven tumor recurrence, 16 (73%) had distant metastases and six (27%) had localized tumors amenable to resection. Three patients (10%) underwent negative, second-look procedures, and all three continued to have elevated CEA levels. In some of their cases re-exploration was done for CEA values exceeding two standard deviations of the nomogram values of the previous observation, although the absolute value and the increase both were quite low: *i.e.*, 1 ng/ml in one case and 2 ng/ml in another. In our own data, we have frequently seen moderate variations in CEA levels and would hesitate to consider exploration for small increases where the baseline is less than 5 ng/ml. At this point, we would recheck blood samples in patients whose CEA has increased about 5 ng/ml and would generally consider re-exploration only if the CEA levels have increased to greater than 10 ng/ml. Holyoke et al. have recommended obtaining three determinations from ten days to two weeks apart, to confirm recurrence.[16] If these values were greater than 2.5 ng/ml and were rising, the possibility of demonstrating recurrence was considered very good by these authors.

Of note, Martin et al. have recently reported a prospective series of second-look surgical procedures selected according to their CEA management protocol. Of 14 patients with colorectal cancer and one with hepatocellular carcinoma, 12 patients (80%) had totally resectable tumor (seven in the pelvis, three in the retroperitoneum and two in the mesentery). Three patients had unresectable tumors in the liver. The average CEA level was 6.5 ng/ml and the time between original surgery and reoperation was 7.5 months. The time delay between a significant CEA elevation and reoperation was 1.5 months. All postsecond-look CEA levels decreased to baseline values. This series has been selected according to a rigorous analysis of CEA elevations and although very encouraging, bears careful scrutiny before being applied in other institutions.

An unanswered question here is the fluctuation of CEA levels in the patient without recurrence. Certain nonmalignant processes have a pronounced effect on CEA and it may be effected by physiologic variation as well. Elevated CEA levels occur in patients with chronic bronchitis, emphysema, ulcerative colitis, regional enteritis and alcoholic cirrhosis.[6,13,27,28,35] Smoking is the most pervasive factor associated with CEA elevations in persons without clinical disease.[1,37] Stevens and Mackay have found a 15% incidence of elevated CEA in normal people smoking over 15 cigarettes per day, compared to 1.5% in age-matched nonsmokers.[37] Alexander et al. have found that mean CEA levels were significantly higher in smokers (2.7 ng/ml) than nonsmokers (1.9 ng/ml), ($p < .001$).[1] Twelve per cent of these smokers versus 5% of nonsmokers had CEA greater than 5 ng/ml, $p < .05$. Although smoking elevated the CEA 0.8 ng/ml regardless of age, there was also a progressive increase of CEA with age in both smokers and nonsmokers. The mean CEA levels in the third versus sixth decades were 1.3 and 1.9 ng/ml in nonsmokers and 1.9 ng/ml and 2.8 ng/ml in smokers.[1] Of importance, the CEA elevated by smoking will return to normal three months after cessation of smoking. In 11 patients with CEA greater than 5 ng/ml (5–14.5 ng/ml), all but one had a decrease to essentially normal values one to three months after cessation of smoking in Alexander's study.[1]

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Discussion

Dr. Richard E. Wilson (Boston, Massachusetts):

I would like to congratulate Dr. Wanebo and his colleagues for their fine presentation and I support their concepts. We have heard at this meeting how valuable thyrocalcitonin and gastrin are as biologic markers for malignant disease. Unfortunately, the relationship of CEA levels to colon cancer is not so specific, nor is the disease itself so amenable to therapy when it recurs.

In reviewing a large series of patients with colorectal cancer operated on for cure at the Peter Bent Brigham Hospital, we have identified that the initial recurrence is regional only one third of the time. Interestingly, though, a large number of the distant metastases were in the liver, and we have heard from Dr. Fortner about the effectiveness of attacking those.

We're particularly interested in identifying ways to make CEA determinations more accurate. Not only are serial values important, but there are also transient elevations in the 10–15 ng/ml range which worry the surgeon, particularly when he's trying to use this as an indication for reresection.

We have found that simultaneous measurement of circulating immune complexes (CIC) in these patients, which are detected by blocking with the serum of an in vitro antibody-dependent cell cytotoxicity assay (ADCC); can be very helpful. When we have seen a parallel rise in blocking, or CIC, and in the CEA, eight out of eight patients have had recurrence.

In another 17 patients with transient rises in CEA that did not have this parallel rise and were not operated on, continued follow-up has failed to show any evidence of recurrence.

We're equally excited by recent data about phytohemagglutinin blastogenesis, which, based on its effect on the lymphocytes of the patient, can also lead to better selection of patients with significant CEA rises.

We have explored 13 patients at the Brigham with rising CEA as the only indicator for exploration, and in four of those cases, curative procedures were possible; another six had effective chemo- or radiotherapy performed, and for three nothing could be done.

Dr. Hiram C. Polk, Jr. (Louisville, Kentucky): I wanted to thank Dr. Wanebo and his associates for bringing to the attention of the Association a subject and a problem that's often been neglected, and surely is an aggravatingly frequent one: The patient who has had a curative resection, and has a recurrence that must be dealt with.

I think he has nicely shown, and corroborated out our own experience, that the CEA examination does have a fair number of false positives—occasionally, it's false negative—and it is expensive. Given the detection, though, I'd like to address the business of retreatment of the recurrence.

Working some time ago with Dr. John Spratt, and again currently, we've taken a very close look at how to detect very favorable early recurrent disease. By "early" we at least mean small. We have been able to do so using clinical means. My reason for rising is simply to indicate that, while our attack on these seemingly favorable recurrences has yielded significant palliation for a large number of the patients, there's not a single one of them that's been rendered free of cancer for more than five years.

Now, I don't mean to say that that doesn't make the effort worthwhile, because there is no question that the palliation that these favorable patients achieve from reoperation for cure exceeded that of anything else we did. I think it does put this in a little bit better perspective. Reresection for cure of a recurrence after a primary operation that's been inadequate, a less-than-standard operation, really is effective, and will occasionally turn a patient cancer negative and cure him. If you're following in the tracks of a standard or an extended standard operation, more often than not this will be palliative at best.

I think it's still an advance, and this puts the paper in better perspective.

Dr. John Minton (Columbus, Ohio): I rise to congratulate Dr. Wanebo for the very delightful presentation, and to briefly ask what makes him decide when to do the second look operations after all the other tests have been negative. This has been a frustrating problem in our series because referring physicians don't want their patients operated upon on the basis of just a rising CEA.

I think the single most important thing is to detect a slowly rising CEA and repeat this observation. Then do the second look at an appropriate time, before the opportunity for resection of recurrent cancer is gone.

(Slide) This is a summary of the first of our two series. A retrospective study was initiated in 1972, and in that group there were 22 patients who had a second-look operation simply for a rising CEA. Under these circumstances we found that there were six patients with local disease. To date, there is one of these six patients alive at five years, three alive into their third year, and the other two have died.

All the patients with distant disease and negative disease at second look have died with recurrent cancer.

The negative diseases in those cases were bony metastases which hadn't presented themselves yet and central nervous system metastases.

The prospective study simply points out that by changing the frequency of CEA evaluation from every three months to every month, we were able to increase the percent of patients who had localized disease at the second-look operation from 25% to 75 per cent. Of course, it's too early to tell anything about long-term benefits in this group of patients, so we can't answer that particular question.

Dr. Donald Lee Morton (Los Angeles, California): Dr. Wanebo has presented a very interesting problem before the Association. Although we all agree that this is a very appealing concept, I think we need to look seriously and carefully at the cost to benefit ratio of the routine use of this approach.

We have a number of patients who had negative explorations after a positive CEA, that is, a rising CEA as the only indication of recurrence. As a result, we are now more cautious and make sure that the CEA continues to rise on repeated samplings. We have patients whose CEA has risen to 10, or even to 14, before it gradually dropped toward normal. Some of these patients have subsequently remained free of disease for as long as four years.

Furthermore, it has yet to be shown whether earlier resection of a recurrence, as detected by elevated CEA, will result in a more significant prolongation of the quality and duration of life than the resection done after clinical detection of recurrence.

I think we have to be cautious in this day of very aggressive treatment for patients with cancer—adjuvant therapy, multimodality therapy, and more aggressive chemotherapy—to wait for the results of careful, prospective trials evaluating cost to benefit relationships, before we begin to apply, as is going on now in a routine fashion, every one of these new tests and procedures to standard surgical practice.

Dr. Harold J. Wanebo (Closing discussion): Regarding Dr. Wilson's comments, I have been familiar with, and have seen a preprint of his work using some ancillary tests to help sharpen the focus of the CEA assay; that is the use of immune blocking factors to help select out a subgroup that have CEA elevations which may be more clinically meaningful. I think this is experimental, of course, and we'll have to see how this develops.

In the same line, I think Dr. Minton's study including his initial retrospective and later prospective data is very exciting. Certainly, with the use of a normogram and earlier selection of patients, his group has been able to detect recurrent disease which is still localized in 70% of the cases. However, we are cautioned both by Dr. Polk and by Dr. Morton, and, I think, quite justly so. That is, can we really accomplish something by resecting recurrent disease at an earlier time?

Dr. Polk has pointed out from his previous work that when you do resect these lesions even earlier, you do not effect long-term cures. Certainly, in this time of adjuvant radiation and chemotherapy, we may be able to augment what we cannot do with surgery alone.

Dr. Morton's point regarding the negative laparotomies is also important. This is a very troublesome area. One of our patients who had a negative laparotomy developed a small myocardial infarct following that procedure but recovered and is currently well. The potential for serious complications with second-look surgery does exist and is all the more serious if these were to occur as the result of a negative exploration.

Regarding our own selection process, as shown in our presentation, we operated on patients that generally had high CEA's, averaging around 20 ng/ml. Our approach now (and this is still evolving) is that if the patient's postoperative CEA has returned to a normal baseline—that is, the 2.5–5 range—we will continue follow-up studies at two to three-monthly intervals. If there is an elevation we will then repeat the study in one month. Of course, it is important here to know the normal variation is one's own laboratory, as modest elevations may be spurious variation only.

If the patient continues to show elevations, and he is not a smoker, then he should be restudied again in one month and if this is significantly elevated, that is, above 10, then he should be evaluated for a second-look procedure.

Treatment of Budd-Chiari Syndrome by Side-to-Side Portacaval Shunt: Experimental and Clinical Results

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The Budd-Chiari syndrome caused by occlusion of the major hepatic veins, often of unknown etiology, is typically characterized by massive ascites, hepatomegaly and abdominal pain due to intense congestion of the liver. The outcome has almost always been fatal. This report describes an evaluation of side-to-side portacaval shunt in dogs with experimental Budd-Chiari syndrome and in six patients with hepatic vein thrombosis. In the animal studies, side-to-side portacaval shunt was very effective in relieving massive ascites, hepatomegaly, hepatic congestion and portal hypertension produced by ligation of the hepatic veins. Only one of 24 dogs with side-to-side anastomosis reformed ascites, 67% of the animals survived until the study was concluded after one year, and liver biopsies showed reversal of the severe pathologic abnormalities. In contrast, all 20 control dogs subjected to a sham laparotomy, and all 20 dogs that underwent end-to-side portacaval shunt reformed massive ascites and died within six months with continued hepatic congestion and necrosis.

All six patients with the Budd-Chiari syndrome due to hepatic vein occlusion had massive ascites (4.4–15.9 l), hepatomegaly, abdominal pain and disturbed liver function. In all six, angiography demonstrated occlusion of the hepatic veins with a patent inferior vena cava (IVC) and a normal IVC pressure, and liver biopsy showed intense centrilobular congestion and necrosis. The most valuable diagnostic study was angiography of the IVC and hepatic veins with pressure measurements. Side-to-side portacaval shunt was performed from four to 14 weeks after the onset of symptoms, and produced dramatic and sustained relief of ascites in five of the six patients during follow-up periods of from eight months to seven years. Liver function returned to normal, hepatosplenomegaly disappeared, none of the survivors developed portal-systemic encephalopathy, and follow-up liver biopsies showed disappearance of congestion and necrosis, but mild to moderate fibrosis. One patient died following an emergency IVC thrombectomy and portacaval shunt, which was undertaken when, during the course of his workup, his condition deteriorated suddenly because the thrombotic process extended from the hepatic veins into the IVC. The everpresent risk of this complication, and the dangers associated with delaying operation were emphasized by this case. It is concluded that side-to-side portacaval shunt, which decompresses the liver by converting the portal vein into an outflow tract, provides effective treatment of the Budd-Chiari syndrome when the occlusive process is confined to the hepatic veins.

THE CLINICAL DISORDER caused by occlusion of the major hepatic veins or the inferior vena cava at the level of the hepatic vein ostia is known as the Budd-Chiari syndrome. Although a brief discussion of this disorder first appeared in the book by Budd in 1845, the first case is said to have been reported by Lambron in 1842.[9] In 1899, in a report of ten collected cases and three personal cases, Chiari[11] presented the first thorough clinical and pathological description of the syndrome, including the hypothesis that it is caused by endophlebitis of the hepatic veins. However, the weight of evidence and current opinion favors the view that the primary process is usually thrombotic rather than inflammatory. Since publication of the initial description, over 500 cases have been reported in the medical literature.

The clinical manifestations of hepatic vein occlusion usually consist of ascites, hepatomegaly and abdominal pain due to intense congestion of the liver caused by obstruction of hepatic venous outflow. Depending on the rapidity and extent of hepatic vein occlusion, the course of the syndrome may be rapid or chronic, progressing to death in a matter of weeks or leading to death from liver failure or bleeding esophageal varices after an illness of months or occasionally years. A rapid course is more common, and the outcome has been fatal in the great majority of reported cases.[21,45,46,58,60]

No cause of the hepatic vein occlusion has been identified in 60–70% of the reported cases.[21,45,56,58,60] In the relatively small number of cases in which the etiology has been proven or suspected, the primary etiologic conditions have included polycythemia rubra vera, invasion of the inferior vena cava and hepatic

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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Supported in part by USPHS Grant AM 12280.

0003-4932/78/1000/0494 $01.65 © J. B. Lippincott Company

veins by malignant neoplasms, paroxysmal nocturnal hemoglobinuria, ingestion of oral contraceptives, trauma, pregnancy, leukemia, sickle cell anemia, ulcerative colitis, hydatid disease and schistosomiasis.[2,25,26,45–47,52,58,62] Membranous obstruction of the inferior vena cava just below the level of the diaphragm has been reported recently with considerable frequency, mainly from Japan, as a cause of a chronic form of Budd-Chiari syndrome.[16,24,27,51,63] The therapeutic implications of this condition as well as of other forms of inferior vena cava occlusion are distinctly different from those of occlusion confined to the major hepatic veins.

Use of side-to-side portacaval shunt, or its hemodynamic equivalents such as splenorenal shunt, mesocaval shunt and mesocaval H-graft, to relieve the Budd-Chiari syndrome caused by occlusion of the hepatic veins has been described sporadically during the past three decades.[4,5,18–20,30,35,40,48,54] The rationale for the use of this procedure is based on substantial evidence that the valveless portal vein can be converted to an outflow tract by an in-continuity anastomosis with the systemic venous system, thereby decompressing the obstructed hepatic vascular bed.[6,7,10,31,32,37–39,41,57,61] However, a thorough trial of side-to-side shunt in the treatment of the Budd-Chiari syndrome has not been conducted, mainly because the condition is uncommon and often the diagnosis has not been made until near or after death.

This report describes the results of an experimental evaluation of side-to-side portacaval shunt in the Budd-Chiari syndrome produced in dogs by ligation of the hepatic veins. On the basis of the experimental results, side-to-side portacaval anastomosis has been used to treat six patients with hepatic vein thrombosis, and the clinical studies in these patients are described. Although the number of patients is small, this report describes the largest clinical experience to date with the use of side-to-side portacaval shunt in the therapy of Budd-Chiari syndrome.

Materials and Methods

Production of Budd-Chiari Syndrome

Our method of producing the Budd-Chiari syndrome in dogs by direct ligation of the hepatic veins has been described in detail in previous reports.[42,43,56] Briefly, it consisted of ligation and division of all hepatic veins except the large left hepatic vein (superior hepatic vein), which was loosely surrounded by an ameroid constrictor (Fig. 1). The ameroid constrictor consisted of a hygroscopic casein plastic disc 22 mm in diameter, 8 mm thick and containing a triangular opening that was 15

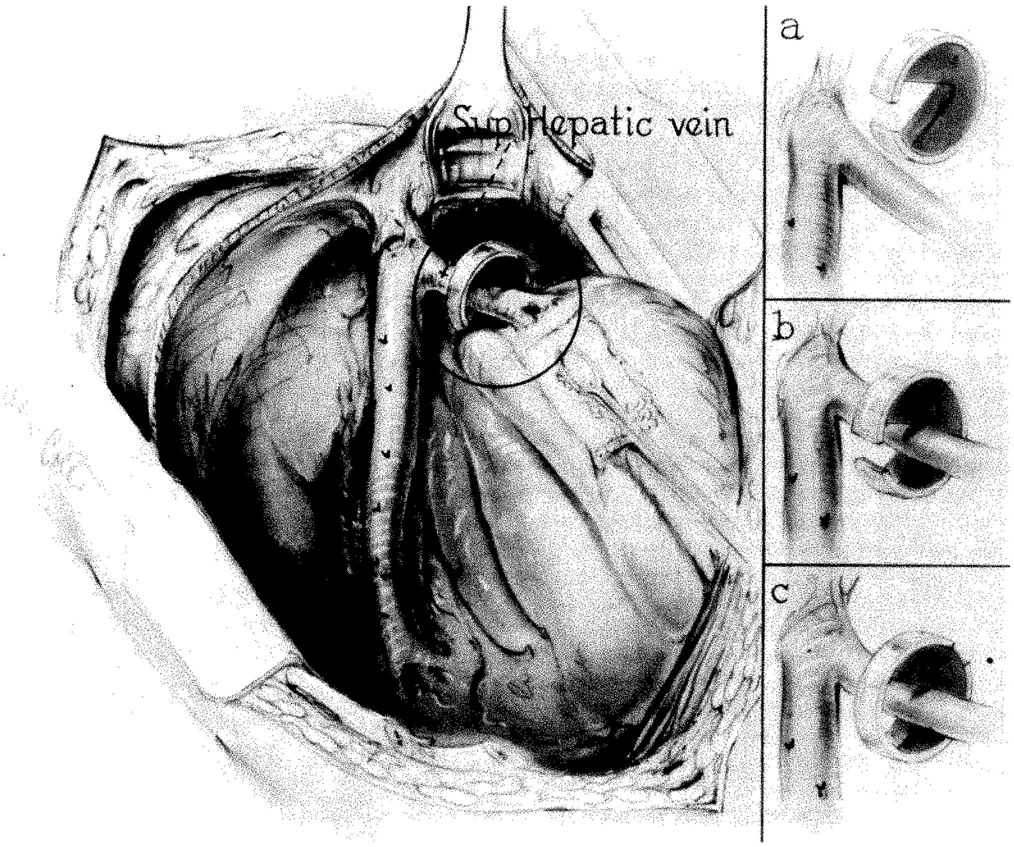

FIG. 1. Technique of induction of Budd-Chiari syndrome in dogs by ligation and division of all hepatic veins except the large superior hepatic vein (left hepatic vein) which was surrounded by an ameroid constrictor.

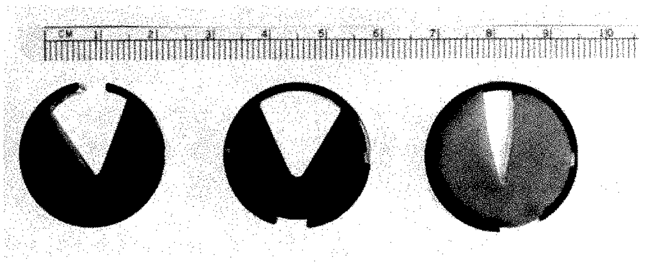

FIG. 2. Ameroid constrictor made of a casein plastic disc surrounded by a stainless steel rim used for gradual occlusion of the left hepatic vein. On the left the ameroid is in position for insertion around the vein. In the middle the ameroid is in the locked position (after insertion around the vein) with the plastic disc rotated so that its slit is at a distance from the slit in the steel rim. On the right is an ameroid removed 35 days after insertion in a dog; the hygroscopic casein plastic has swelled resulting in narrowing of the slit and occlusion of the vein.

mm wide at the periphery and 15 mm deep to accomodate the left hepatic vein. The solid casein plastic disc was encased in a stainless steel rim 2 mm in wall thickness with a 5 mm-wide slit to allow placement around the intact vein (Fig. 2). After insertion of the ameroid around the vein, it was locked in place by rotation of the opening in the plastic disc to a point distant from the slit in the steel rim. At the time of insertion, the ameroid did not initially constrict the left hepatic vein. However, the lumen in the ameroid gradually narrowed as the hygroscopic casein plastic swelled centrally so that severe hepatic outflow block, portal hypertension and massive, intractable ascites developed within several weeks. Previous studies in over 200 dogs showed that the left hepatic vein was completely occluded within 35–53 days, and that every animal developed massive ascites.

Experimental Groups

Hepatic vein ligation was performed in 70 mongrel dogs that weighed from 20 to 29 kg. Six dogs died within one month after operation. Two months postoperatively, when ascites was well-established in all animals, the remaining 64 dogs were randomly divided into three groups as follows:

Group I was made up of 20 dogs that underwent a *sham laparotomy* which involved dissection of the portal vein and inferior vena cava and all other technical maneuvers preparatory to performance of a portacaval anastomosis without actual construction of the shunt. Five of these animals died within one month postoperatively, all with massive ascites, and 15 were long-term survivors.

Group II consisted of 20 dogs that were subjected to an *end-to-side portacaval shunt* which was designed by delineation with calipers to measure 2.0 × 0.5 cm. Five of these dogs died within one month after the shunt procedure, all with massive ascites, and 15 were long-term survivors.

Group III contained 24 dogs that underwent a *side-to-side portacaval shunt* of identical size to the end-to-side anastomosis. Six of these animals died within one month after operation and 18 were long-term survivors. None of the dogs in this group that died during the early postoperative period had ascites.

Animals that survived for one year after sham laparotomy or portacaval shunt underwent a sacrifice operation. The volume of ascites was measured at the time of the second operation and again at the time of death or sacrifice. Pressures in the portal vein and abdominal inferior vena cava were measured by needle puncture, using a saline manometer, at the beginning and end of each operation, and at the time of sacrifice in surviving dogs. The level of the inferior vena cava was used as the reference baseline. Liver biopsies were obtained for microscopic examination at each operation and at death. Autopsies were performed in all animals and included determinations of the completeness of hepatic vein occlusion and the patency and size of the portacaval shunts.

Results

Mortality Rate

Table 1 shows the mortality rates in the three groups of dogs. The one month or operative mortality rate was 25% in each group. All of the dogs that died shortly after sham laparotomy or end-to-side portacaval shunt had massive ascites, while none of the animals that died within one month of side-to-side portacaval shunt reformed ascites.

The 15 long-term survivors in Group I died within 60 to 185 days after sham laparotomy, a six month mortality rate of 100%. Similarly, the six month mortality rate after end-to-side portacaval shunt in Group II was 100%, with all of the 15 long-term survivors dying within 50 to 172 days after the operation. In contrast, of

TABLE 1. *Mortality Rates in Dogs with Budd-Chiari Syndrome Following Sham Laparotomy, End-to-side Portacaval Shunt and Side-to-side Portacaval Shunt*

Group	No. Dogs	Operative (1 month) Mortality Rate-%	One Year Mortality Rate-% (excludes operative deaths)
I Sham laparotomy	20	25%	100%
II End-to-side shunt	20	25%	100%
III Side-to-side shunt	24	25%	33%

TABLE 2. *Reaccumulation of Ascites in Dogs with Budd-Chiari Syndrome Following Sham Laparotomy, End-to-side Portacaval Shunt and Side-to-side Portacaval Shunt*

		Ascites at Operation			Ascites at Autopsy		
			Volume-L			Volume-L	
Group	No. Dogs	% of Group	Mean	Range	Reaccumulation % of Group	Mean	Range
I Sham laparotomy	20	100	3.2	2.2–5.3	100	3.4	1.4–7.2
II End-to-side shunt	20	100	3.0	2.0–5.7	100	3.8	1.6–6.8
III Side-to-side shunt	24	100	3.3	2.5–6.2	4	1.4	1.4

the 18 long-term survivors of side-to-side portacaval shunt in Group III, 12 lived until the time of sacrifice one year postoperatively, a one year mortality rate of 33%. The period of survival of the six dogs in Group III that failed to live for one year ranged from 94 to 324 days.

Ascites

All of the dogs developed substantial ascites following hepatic vein ligation, and the volume measured at the time of sham laparotomy or portacaval shunt was similar in the three groups. All dogs rapidly reformed ascites following either sham laparotomy or end-to-side portacaval shunt and the ascites persisted until death (Table 2). The mean volume of ascites at the time of autopsy was 3.4 L. in Group I and 3.8 L. in Group II. In striking contrast, only one of the 24 dogs in Group III reaccumulated ascites following side-to-side portacaval shunt. This animals died 182 days postoperatively and no distinct cause for the ascites was identified at autopsy. It is noteworthy that none of the dogs in Group III that survived to the end of the study period had ascites when they were sacrificed after one year.

Pressures

Table 3 shows the results of pressure measurements in the portal vein and inferior vena cava at each operation and, in Group III, at the time of sacrifice one year after portacaval shunt. The portal pressure was normal in all dogs at the time of hepatic vein ligation. By the time of the second operation when the Budd-Chiari syndrome was well established, all of the dogs had portal hypertension, and the magnitude was similar in the three groups. Both the end-to-side and side-to-side portacaval shunts reduced the portal pressure to the normal range. Hepatic sinusoidal pressure was not measured, although it is well established that in the presence of hepatic outflow block the side-to-side anastomosis is substantially more effective than the end-to-side shunt in overcoming intrahepatic hypertension.[50,61] At the time of the sacrifice operation one year postoperatively, the portal pressure was normal in the ten dogs with side-to-side shunt in which pressure measurements were performed.

Liver Biopsies

Prior to hepatic vein ligation the liver in all dogs was normal as shown by gross and microscopic examinations. At the time of the sham laparotomy or shunt when the Budd-Chiari syndrome was well-established, all livers were enlarged to from two to four times normal size and appeared congested and friable. Liver biopsies at this time showed intense centrilobular congestion, necrosis of cells around the central veins, dilated lymphatics and subcapsular edema (Fig. 3). In the dogs in Group I, these gross and microscopic abnormalities were unchanged at the time of death, and substantial

TABLE 3. *Portal Vein (PV) and Inferior Vena Cava (IVC) Pressures in Dogs Before and After Induction of Budd-Chiari Syndrome, and After Portacaval Shunt (Mean and range of pressures shown in mm saline)*

		Initial		Massive Ascites		After Shunt		After 1 Year*	
Group	No. Dogs	PV	IVC	PV	IVC	PV	IVC	PV	IVC
I Sham laparotomy	20	112 (82–124)	62 (28–94)	242 (204–302)	94 (82–112)	—	—	—	—
II End-to-side shunt	20	115 (76–130)	67 (32–94)	256 (198–312)	102 (78–143)	130 (112–148)	126 (102–140)		
III Side-to-side shunt	24	114 (72–128)	63 (31–90)	247 (208–300)	97 (68–132)	122 (108–142)	117 (106–139)	97 (74–112)	92 (70–110)

* 10 dogs

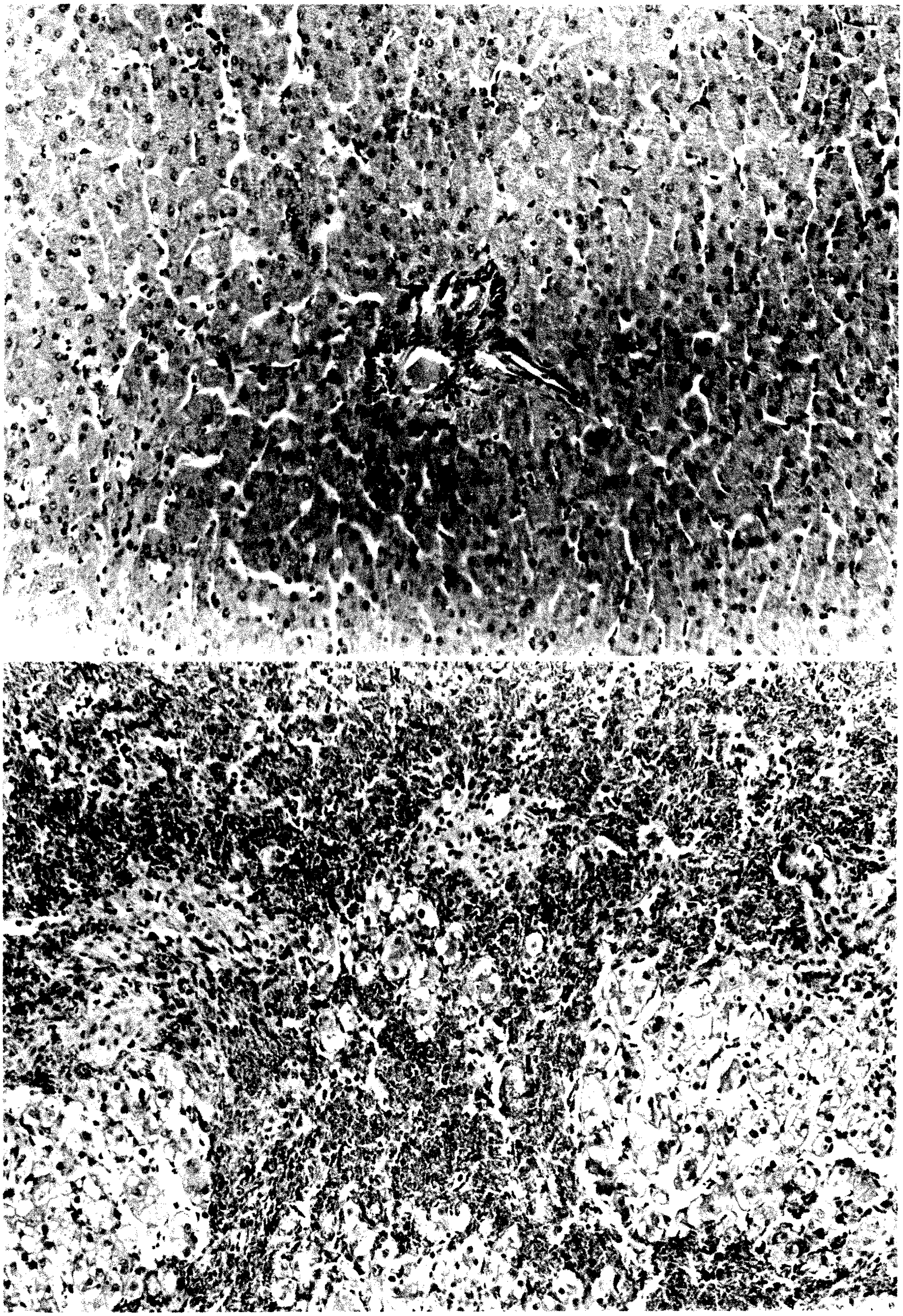

FIG. 3. Photomicrographs of liver biopsies obtained from a dog (top) before hepatic vein ligation when the liver was normal, and (bottom) at the time of portacaval shunt when the Budd-Chiari syndrome was well established and ascites was massive. There is intense congestion and necrosis of the hepatic parenchyma in the biopsy shown in the bottom panel. (× 140).

fibrosis was found in many of the liver biopsies. Similarly, all of the dogs in Group II had hepatomegaly at the time of death, and severe congestion, necrosis and fibrosis were found in all liver biopsies, although in 38% of the animals, the microscopic picture was less severe than at the time of the shunt operation. Only one dog with a side-to-side shunt in Group III, the single animal with ascites, had an enlarged liver and microscopic findings of congestion and necrosis at the time of death. The other 23 dogs in Group III had a liver that was normal in size and gross appearance at autopsy; liver biopsies were normal in 35 per cent of these dogs and showed minimal fibrosis in the remaining 65 per cent.

At autopsy, the hepatic veins were occluded in every animal in the study. All portacaval shunts were found to be widely patent.

Clinical Studies

Patients

On the basis of the results of our experimental studies showing that side-to-side portacaval anastomosis was very effective in relieving hepatic outflow block, massive ascites and portal hypertension produced by occlusion of the hepatic veins, we have performed side-to-side portacaval shunt in six patients with Budd-Chiari syndrome caused by thrombosis of the hepatic veins. Four were men and two were women, and their ages ranged from 19 to 45 years. All of the patients had been in good health prior to the onset of symptoms. One patient was found to have polycythemia rubra vera and another had been taking oral contraceptives for five years. In the remaining four patients no condition known to be associated with hepatic vein thrombosis was identified.

Symptoms and Signs

Table 4 summarizes the symptoms and signs in the six patients. The initial symptom in all six was abdominal distention which increased progressively during the course of a few weeks. All of the patients had abdominal pain that was dull, nagging and chronic. The pain was localized to the right hypochondrium in one patient, diffuse in the upper abdomen in three and diffuse throughout the abdomen in two. All of the patients had anorexia and progressive weakness. One-half of the patients noticed mild jaundice, two developed intermittent vomiting, one had diarrhea and one observed fever to 101°F. The symptoms were of sufficient severity to cause the patients to consult a physician within four weeks of their onset, and usually sooner.

Physical examination performed on admission to our institution from three weeks to three months after the onset of symptoms showed massive ascites, hepatomegaly and substantial wasting due to loss of lean body mass in all patients. All of them appeared chronically and seriously ill. Three patients had mild jaundice, three had distention of the superficial veins of the anterior abdominal wall and one had low grade fever. The spleen was palpable in only two patients although it was subsequently shown to be enlarged in all six. None of the patients had edema of the lower extremities or lower trunk, a finding that indicates involvement of the inferior vena cava in the occlusive process.

Diagnostic Studies

An extensive diagnostic evaluation was performed in all patients (Table 5). The diagnostic study of greatest value was angiographic examination of the inferior vena cava (IVC) and hepatic veins, with pressure measurements. This study was combined with hepatic and superior mesenteric arteriography and indirect portography. All patients were shown to have a patent IVC with a pressure that was within the normal range for subjects with ascites (62–126 mm saline) (Fig. 4). Patency of the IVC is a prerequisite for portacaval shunt so that this finding was of crucial importance. In three patients, the IVC was moderately compressed in its intrahepatic course by the enlarged liver, a finding that has been reported previously[13,28,49,58] and usually is not of clinical significance (Fig. 6A). In all patients, hepatic venography demonstrated occlusion of the major hepatic veins, a diagnostic finding. It was not always possible to catheterize all of the hepatic veins because of complete occlusion, but at least one major hepatic vein

TABLE 4. *Symptoms and Signs in Six Patients with Budd-Chiari Syndrome*

Symptoms	% of Group	Signs	% of Group
Abdominal Distention	100	Massive Ascites	100
Abdominal Pain	100	Hepatomegaly	100
Weakness	100	Wasting	100
Anorexia	100	Jaundice	50
Jaundice	50	Abdominal Venous Distention	50
Vomiting	33		
Diarrhea	17	Splenomegaly	33
Fever	17	Fever	17

TABLE 5. *Results of Diagnostic Studies in Six Patients with Budd-Chiari Syndrome*

	% of Group		% of Group
Angiography & Pressures		Liver Biopsy (3 patients studied)	
Patent IVC	100	Centrilobular congestion	100
Occluded hepatic veins	100	Centrilobular necrosis	100
Stretched hepatic arteries	100	Abnormal Liver Function Tests	
Patent portal vein	100	Bromsulphalein retention (23–90%)	100
Normal IVC pressure	100	Serum alkaline phosphatase (148–345 IU)	100
Elevated WHVP (3 patients studied)	100	Prothrombin time (13–16.5 sec.)	83
Scintiscan		Serum albumin (2.1–2.8 g/dl)	83
Decreased hepatic uptake	100	Serum bilirubin (3.9–4.5 mg/dl)	50
Inhomogeneous hepatic uptake	100	SGOT (142–540 IU)	50
Central hot spot in liver	33	Normal Upper Gastrointestinal X-Rays	100

was entered in every patient. Injection of dye in the wedged position demonstrated the characteristic spider web pattern of small hepatic venous collaterals in four patients (Fig. 5). In all six patients, hepatic arteriography demonstrated the nonspecific abnormality of stretching and attenuation of the branches of the hepatic artery within the liver, and indirect portography showed a patent portal vein. These findings were not of great importance but were helpful. Wedged hepatic vein pressure (WHVP) was measured in three patients and was markedly elevated in all three, ranging from 344 to 442 mm saline.

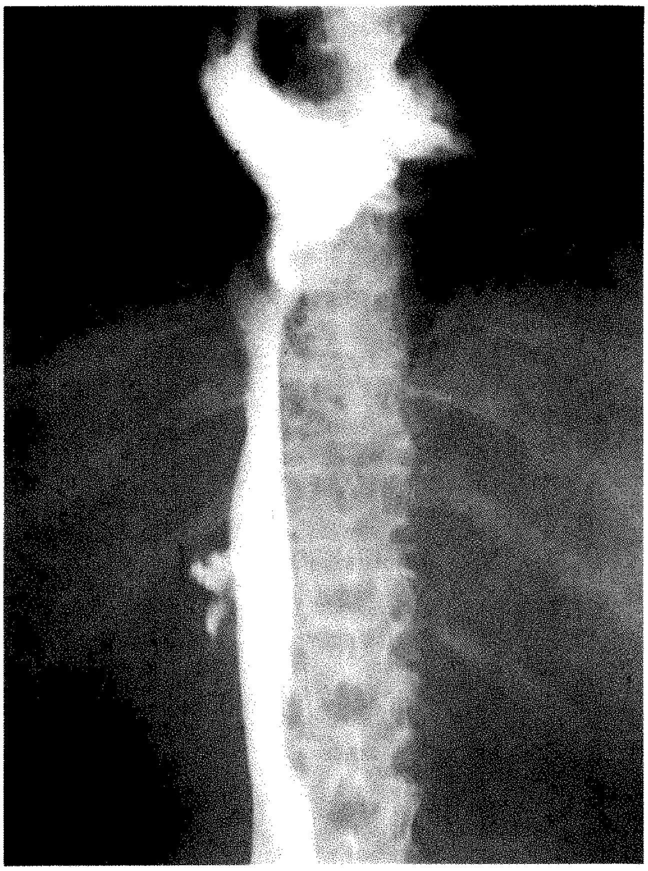

FIG. 4. Inferior venacavogram in case 3 showing a widely patent IVC. IVC presure was 62 mm saline.

Needle liver biopsy was not performed in every patient because the clinical picture and results of other studies, particularly angiography, justified confidence in the diagnosis of Budd-Chiari syndrome. However, prior to admission to our institution referring physicians performed a needle liver biopsy in two patients and an open liver biopsy in one patient, and in each instance the microscopic picture of intense centrilobular congestion and necrosis was observed. These findings strongly suggested the diagnosis of Budd-Chiari syndrome.

Scintiscans of the liver and spleen with ^{99m}Tc sulfur colloid were obtained in all patients and showed the nonspecific abnormalities of decreased and inhomogeneous hepatic uptake of radiocolloid, increased uptake of radiocolloid by the spleen and bone marrow, and hepatosplenomegaly. Central localization of radiocolloid in the liver, which has been reported to be of diagnostic importance,[36,58] was observed in only two patients.

Abnormal results of liver function tests were obtained in all patients, although the type of abnormality was somewhat variable. All patients had marked retention of bromsulphalein ranging from 23 to 90% in 45 minutes, and elevation of serum alkaline phosphatase ranging from 148 to 345 IU (normal 25–85 IU). Five of the six patients had a prolonged prothrombin time and decreased serum albumin concentration ranging from 2.1 to 2.8 g/dl. Three patients had elevation of the serum glutamic oxalacetic transaminase (SGOT) ranging from 142 to 540 IU, and three had moderate elevations of serum bilirubin ranging from 3.9 to 4.5 mg/dl.

Barium contrast upper gastrointestinal x-rays were normal in all patients.

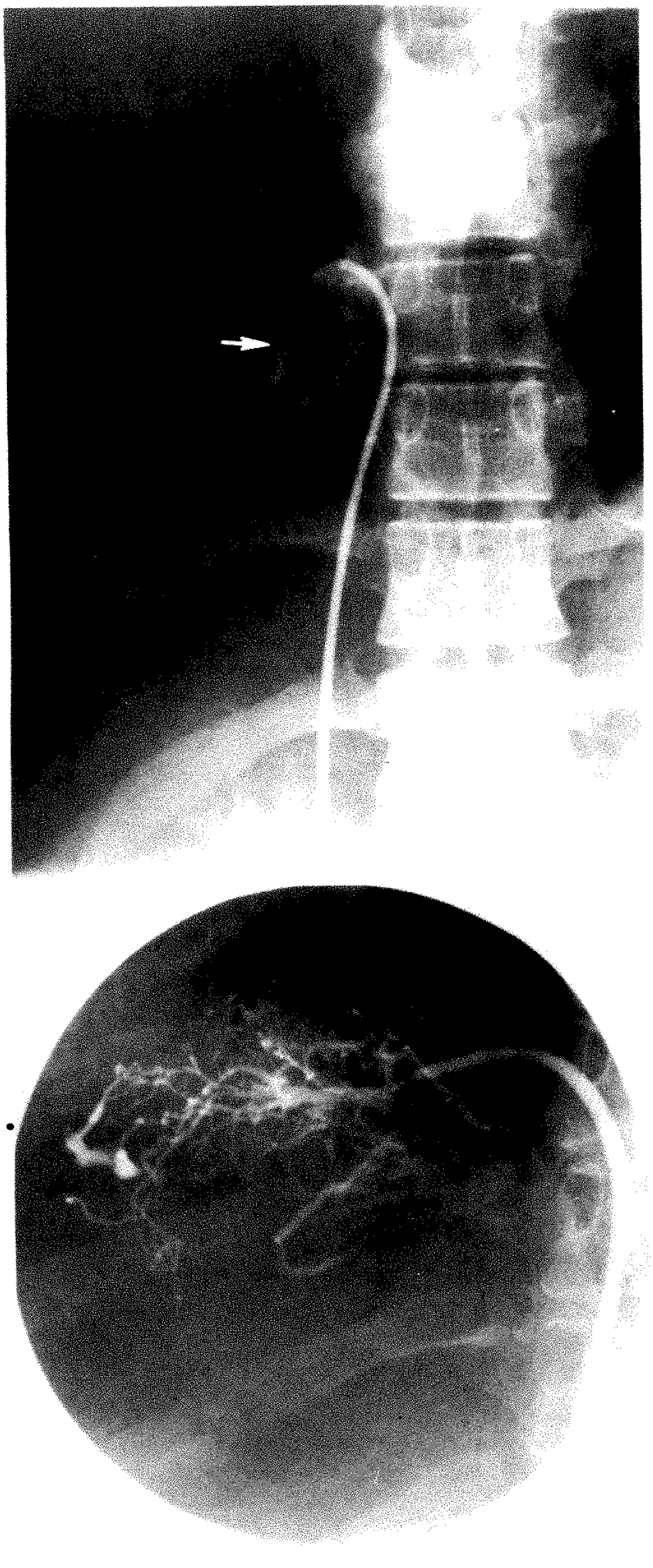

FIG. 5. Hepatic venogram in case 2 showing (top) filling defects (thrombi) in the right hepatic vein occupying much of the lumen and (bottom) a typical spider web network of small venous collaterals on injection of dye in the wedged position. The left hepatic vein was completely occluded.

Findings at Operation

Side-to-side portacaval shunt was performed from four to 14 weeks after the onset of the illness. In five of the six patients the shunt operation was straightforward, since it was demonstrated preoperatively that the IVC was patent and the thrombotic process was confined to the hepatic veins. In the remaining patient (see case 6 below) initial angiography showed a patent IVC but repeat angiographic studies, performed shortly before operation because the patient suddenly developed edema of the lower extremities and trunk, showed extension of thrombus into the IVC with sudden elevation of IVC pressure (Fig. 6). An emergency IVC thrombectomy and portacaval shunt was undertaken in a desperate attempt to reverse a rapidly downhill course.

At operation massive ascites ranging in volume from 4.4 to 15.9 l, an enlarged and congested liver and splenomegaly were found in all patients (Table 6). The IVC pressure (IVCP) was normal in five of the six patients, ranging from 74 to 120 mm saline. The sixth patient (case 6 below) was known preoperatively to have developed sudden thrombosis of the IVC and had an IVCP of 250 mm saline. All patients had portal hypertension with free portal pressures (FPP) ranging from 265 to 434 mm saline. Hepatic occluded portal pressure (HOPP) was markedly elevated in all patients, and in two it was higher than FPP. Splanchnic occluded portal pressure (SOPP) showed the usual reciprocal relationship to HOPP. Side-to-side portacaval shunt reduced the portal pressure to the normal range (134 to 175 mm saline) in the five patients whose IVC was patent. The pressure gradient across the shunt was 10 mm. saline or less in all patients.

A wedge liver biopsy obtained at operation showed intense centrilobular congestion and intense centrilobular necrosis in all patients (Fig. 7). Five of the six patients had mild to moderate hepatic fibrosis.

Results of Side-to-Side Portacaval Shunt

Table 7 summarizes the long-term results of side-to-side portacaval shunt. The patient who underwent emergency IVC thrombectomy and portacaval shunt because of sudden extension of thrombosis into the IVC (case 6 below) died six days postoperatively with multiorgan failure and recurrence of IVC thrombosis. The remaining five patients were alive and well when last seen from eight months to seven years postoperatively. A striking feature of the early recovery period was a rapid gain in lean body weight that ranged from 24 to 40 pounds in a period of three to six months.

TABLE 6. *Findings at Operation in Six Patients with Budd-Chiari Syndrome*

				Pressures—mm Saline						Operative Liver Biopsy—0 to 4+		
				Preshunt				Postshunt				
Case	Ascites L.	Hepatomegaly	Splenomegaly	IVCP	FPP	HOPP	SOPP	IVCP	FPP	Centrilobular Congestion	Centrilobular necrosis	Fibrosis
1	8.4	+	+	92	428	440	420	144	150	4+	4+	0
2	7.4	+	+	86	360	364	352	152	156	4+	4+	2+
3	4.4	+	+	74	358	326	390	134	138	4+	4+	1+
4	8.7	+	+	112	342	338	348	168	176	4+	4+	2+
5	6.0	+	+	120	265	200	305	175	165	4+	4+	1+
6	15.9	+	+	250	434	486	422	284	289	4+	4+	2+

All of the survivors have remained free of ascites without requiring diuretic therapy. Results of periodic liver function tests have been consistently normal. None of the patients have developed portal-systemic encephalopathy or required restriction of dietary protein, probably because they have good hepatic function. Hepatosplenomegaly has disappeared in all patients.

Liver biopsies and angiographic studies with pressure measurements were performed periodically in the four survivors whose follow-up exceeded one year. The results are summarized in Table 8. There was no evidence of congestion or necrosis in any of the liver biopsies, but mild to moderate fibrosis was observed in all. Angiography demonstrated patency of the portacaval shunt and IVC, and pressure measurements showed a wide open anastomosis with a gradient of 14 mm saline or less across the shunt. It was not possible to catheterize the hepatic veins in any patient, presumably because they were completely occluded.

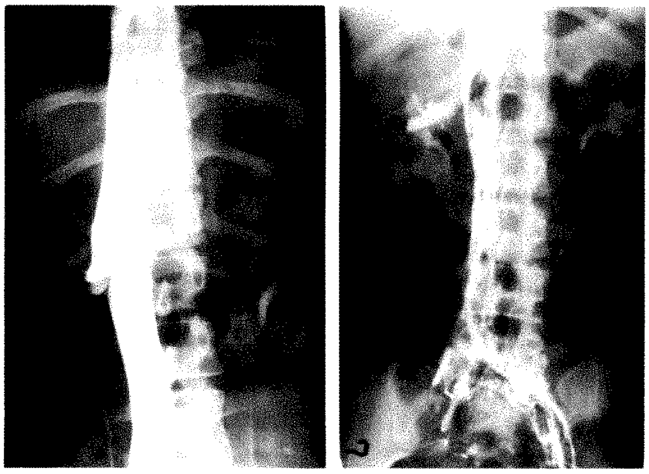

FIG. 6. Inferior venacavogram in case 6 showing (left) a widely patent IVC with side-to-side compression in its intrahepatic course by the swollen liver. Hepatic venography (not shown) demonstrated occlusion of the major hepatic veins. An angiographic study performed 12 days later (right) shows extension of thrombosis throughout the iliac veins and IVC. Extension of the thrombotic process into the IVC caused sudden deterioration of the patient's condition, and an emergency attempt at IVC thrombectomy and portacaval shunt failed.

Case Reports

Case 1. This 28-year-old previously healthy white male was admitted to the hospital with a five week history of progressive increase in abdominal girth, persistent pain in the right upper abdomen, progressive weakness and anorexia, and a one week history of jaundice and intermittent vomiting. Symptoms had progressed despite treatment with diuretics and bed rest for one month by his family physician. On physical examination he appeared chronically ill with substantial loss of lean body mass and had jaundice, marked ascites, hepatomegaly, splenomegaly and distended superficial abdominal veins. There was no peripheral edema. Extensive blood studies showed the following abnormalities: serum bilirubin 4.5 mg/dl, serum alkaline phosphatase 240 IU (normal 25–85 IU), bromsulphalein retention 42% in 45 minutes, prothrombin time 14 seconds (control 11 seconds), partial thromboplastin time 45 seconds (control 33 seconds), and serum albumin 2.3 g/dl. Scintiscans showed hepatosplenomegaly with diminished and inhomogeneous hepatic uptake of radiocolloid and an area of concentrated uptake in the center of the liver. Barium contrast upper gastrointestinal x-rays were normal. Angiogiographic studies showed a patent IVC with moderate compression in its intrahepatic course by the enlarged liver, occlusion of the major hepatic veins with a spider web pattern of abnormal vessels on wedged hepatic venography, stretching and narrowing of the branches of the hepatic artery and a normal portal vein (PV). IVCP was 104 mm saline and WHVP was 442 mm saline. A diagnosis of Budd-Chiari syndrome with thrombosis of the hepatic veins of unknown etiology was made.

A side-to-side portacaval shunt was performed six weeks after the onset of symptoms. The findings at operation were 8.4 liters of ascites, marked enlargement and congestion of the liver, splenomegaly, and the following pressures in mm saline: IVCP 92; FPP 428; HOPP 440; SOPP 420. Following construction of the portacaval anastomosis the pressures were: IVCP 144; FPP 150. A liver biopsy showed intense congestion and substantial necrosis in the center of the lobule.

The postoperative course was uncomplicated and the patient was discharged from the hospital 18 days after operation. He resumed normal activity and employment after three months, and remained free of ascites without diuretic therapy during seven years of follow-up. Within six months of operation he gained 38 pounds in lean body weight. Results of liver function tests performed each year were normal. There has been no evidence of portalsystemic encephalopathy. A needle liver biopsy performed five years postoperatively showed moderate fibrosis but no necrosis or congestion. Angiographic studies performed five years after operation showed a widely patent portacaval anastomosis and IVC, and the following pressure measurements in mm. saline: IVCP 108; FPP 114. It was not possible to catheterize the hepatic veins and it was assumed that they were completely occluded.

Case 2. This 45-year-old white female was transferred from another hospital where she had been hospitalized for three weeks. She gave a three month history of progressive abdominal distention,

TABLE 7. *Outcome of Six Patients with Budd-Chiari Syndrome Who Underwent Side-to-side Portacaval Shunt*

			Follow-up				
Case	Primary Condition	Duration—Onset to Operation (Wks.)	Years	Ascites	Need for Diuretics	Liver Function Tests	Encephalopathy
1	Unknown	6	7	0	0	Normal	0
2	Unknown	14	6	0	0	Normal	0
3	Oral contraceptives	7	4	0	0	Normal	0
4	Unknown	9	3	0	0	Normal	0
5	Unknown	4	⅔	0	0	Normal	0
6	Polycythemia vera	14	Died—6 days	—	—	—	—

persistent upper abdominal pain, anorexia and progressive weakness, and a one month history of jaundice and intermittent diarrhea. One month prior to the onset of symptoms she had an upper respiratory infection that forced her to stay home from work for one week, but otherwise she had been in excellent previous health. Treatment at the other hospital with prednisone and diuretics based on a presumptive diagnosis of viral hepatitis was unsuccessful. Referral to our institution was stimulated by a needle liver biopsy that showed marked hepatic congestion and necrosis, and was interpreted as indicating Budd-Chiari syndrome. Physical examination on admission to our institution showed marked wasting of lean body mass, jaundice, spider nevi, tense ascites, hepatomegaly and distended superficial abdominal veins. There was no peripheral edema. Extensive blood studies showed the following abnormalities: serum bilirubin 4.2 mg/dl, SGOT 260 IU, serum alkaline phosphatase 174 IU, bromsulphalein retention 38% in 45 minutes, prothrombin time 14.6 seconds (control 10.8 seconds), partial thromboplastin time 52 seconds (control 30 seconds), and serum albumin 2.1 g/dl. Scintiscans showed an enlarged liver and spleen, markedly diminished and inhomogeneous hepatic uptake of radiocolloid, and concentration of radiocolloid in a small central area of the liver. Barium contrast upper and lower gastrointestinal x-rays were normal. Angiographic studies showed a patent IVC with moderate compression of the intrahepatic segment by the enlarged liver, stretching and attenuation of the intrahepatic branches of the hepatic artery, and a normal PV. It was not possible to catheterize the left hepatic vein, but the right hepatic vein showed marked narrowing by filling defects and a network of tiny veins of small caliber. IVCP was 74 mm saline and WHVP was 344 mm saline. A diagnosis of Budd-Chiari syndrome with thrombosis of the hepatic veins of unknown etiology was made.

A side-to-side portacaval shunt was performed 14 weeks after onset of symptoms. The findings at operation were 7.4 l of ascites, an enlarged and congested liver, splenomegaly and the following pressures in mm saline: IVCP 86; FPP 360; HOPP 364; SOPP 352. Post-shunt pressures were: IVCP 152; FPP 156. A liver biopsy showed intense centrizonal congestion and loss of parenchyma and moderate fibrosis between the portal tracts and central veins.

The postoperative course was complicated by a minor wound infection and transient reformation of ascites which responded to diuretic therapy. The patient was discharged from the hospital three weeks after operation and had returned to normal activity after three months. Lean body weight gain amounted to 27 pounds within six months. During six years of follow-up the patient remained free of ascites without diuretic therapy, and repeated liver function tests gave consistently normal results. There have been no manifestations of portal-systemic encephalopathy. A needle liver biopsy performed five years after operation showed only moderate fibrosis. Angiographic studies performed three and six years after operation showed a widely patent portacaval shunt and IVC, but it was not possible to catheterize the hepatic veins, presumably because they were completely occluded. The most recent pressure measurements in mm saline were: IVCP 124; FPP 132.

Case 3. This 30-year-old previously healthy white female was admitted to the hospital because of a six week history of progressive abdominal enlargement, diffuse abdominal pain, fatigue, anorexia and occasional vomiting all of which were initially presumed to be due to pregnancy. She had been taking oral contraceptives regularly for five years. She had shown no response to two weeks of diuretic therapy and bed rest by her family physician. On physical examination she appeared seriously and chronically ill and had moderate wasting of lean body mass, marked ascites, hepatomegaly and splenomegaly. The uterus was normal in size and there was no jaundice or peripheral edema. Extensive blood studies showed the following abnormalities: serum bilirubin 2.0 mg/dl, serum alkaline phosphatase 148 IU, bromsulphalein retention 28% in 45 minutes, prothrombin time 13 seconds (control 10.2 seconds), and serum albumin 2.8 g/dl. Scintiscans showed hepatosplenomegaly with decreased and inhomogeneous hepatic uptake of radiocolloid. Barium contrast upper gastrointestinal x-rays were normal. Angiographic studies showed a widely patent IVC, occlusion of the major hepatic veins by filling defects, stretching and attenuation of the branches of the hepatic artery, and a normal PV. Pressures in mm saline were: IVCP 62 and WHVP 366. A diagnosis of Budd-Chiari syndrome with thrombosis of the hepatic veins related to oral contraceptive therapy was made. During

TABLE 8. *Results of Follow-up Liver Biopsies, Angiography and Pressure Measurements in Four Patients with Budd-Chiari Syndrome Three to Six Years After Portacaval Shunt*

	Liver Biopsy—0 to 4+				Angiography and Pressures (mm Saline)					
Case	Time (Yrs.)	Fibrosis	Congestion	Necrosis	Time (Yrs.)	Patent Shunt	Patent IVC	Occluded Hepatic Veins	IVCP	FPP
1	5	2+	0	0	5	+	+	+	108	114
2	5	2+	0	0	6	+	+	+	124	132
3	4	1+	0	0	4	+	+	+	96	110
4	3	2+	0	0	3	+	+	+	144	158

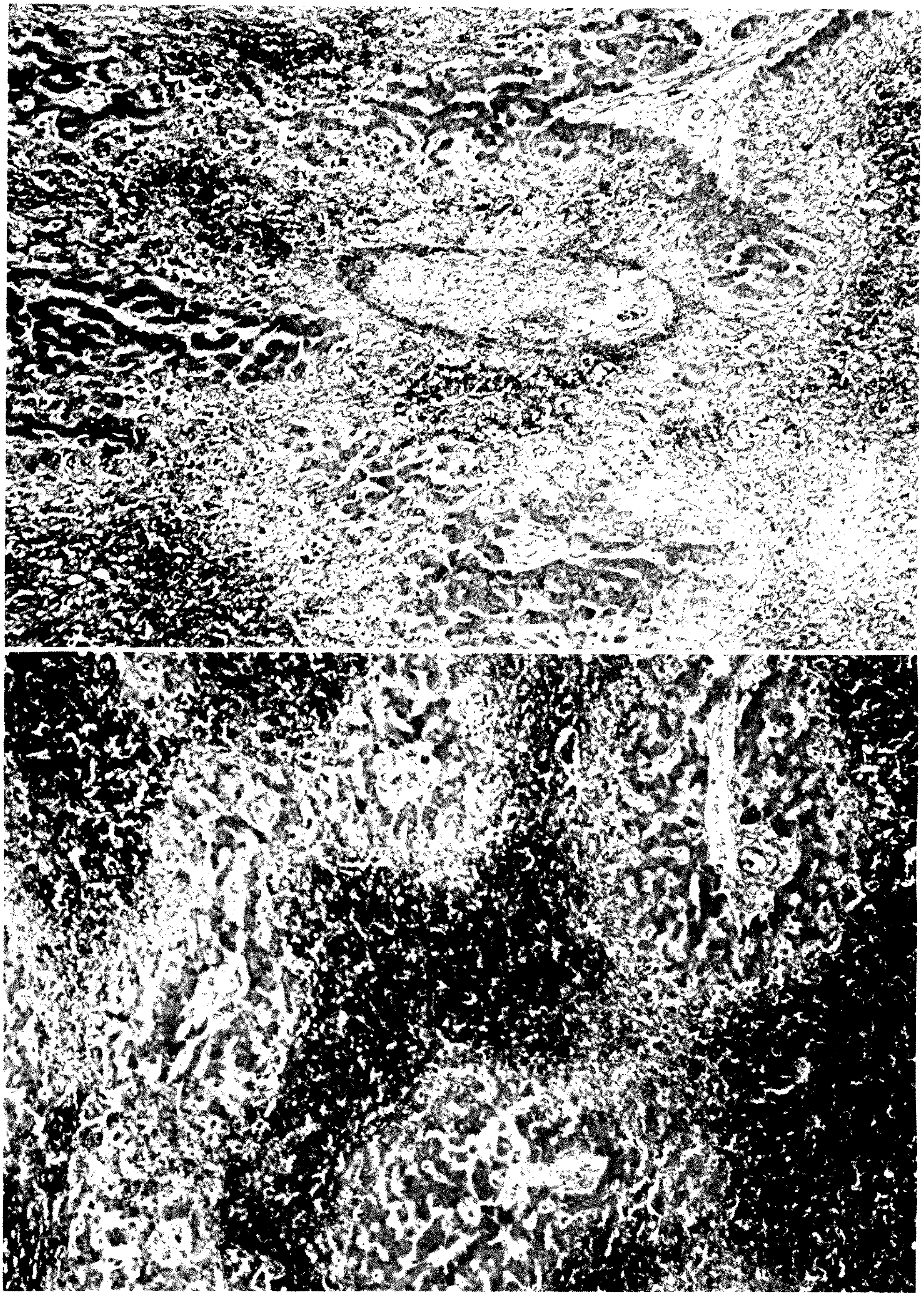

FIG. 7. Photomicrographs of liver biopsies obtained in case 4 (top) and in case 5 (bottom) showing typical picture of intense centrilobular congestion and necrosis, with widespread loss of hepatocytes. A thrombosed hepatic vein is seen in the center of the top panel. (×50)

the initial week of hospitalization her abdominal pain increased, she was unable to eat, weakness progressed and she appeared to be deteriorating.

A side-to-side portacaval shunt was performed seven weeks after the onset of symptoms. The findings at operation were 4.4 l of ascites, a markedly enlarged and congested liver, a moderately enlarged spleen and the following pressures in mm saline: IVCP 74; FPP 358; HOPP 326; SOPP 390. Pressures after construction of the portacaval anastomosis were: IVCP 134; FPP 138. A liver biopsy showed intense contrilobular congestion and necrosis with some fibrosis.

The postoperative course was uncomplicated and the patient was discharged from the hospital 19 days postoperatively. Within three months of discharge she gained 24 pounds in lean body weight and resumed normal activity. During four years of follow-up she remained free of ascites without diuretic therapy, and results of periodic liver function tests were normal. Portal-systemic encephalopathy did not develop. A needle liver biopsy performed four years postoperatively showed normal architecture except for minimal fibrosis. Angiographic studies performed four years after operation showed a widely patent portocaval shunt and IVC. Catheterization of the occluded hepatic veins was not possible despite repeated attempts. Pressure measurements in mm saline were: IVCP 96; FPP 110.

Case 4. This 34-year-old previously healthy white male was transferred from another hospital where he had been hospitalized on two occasions during the preceeding two months. He gave a two month history of progressive abdominal enlargement, intermittent upper abdominal pain, progressive weakness and anorexia. During his initial admission to the other hospital he was found to have hepatomegaly and ascites and was discharged on diuretic therapy, only to be readmitted because of unresponsiveness to treatment and worsening of his condition. A diagnosis of Budd-Chiari syndrome of unknown etiology was made during the second admission to the other hospital on the basis of a needle liver biopsy showing marked centrilobular congestion and necrosis, and angiographic studies that showed a patent IVC with a pressure of 106 mm saline, almost complete occlusion of the right and left hepatic veins with collateral vessel formation, distortion of the branches of the hepatic artery and a normal PV. Physical examination on admission to our institution showed marked wasting, tense ascites, hepatomegaly and distended superficial abdominal veins. There was no jaundice or peripheral edema. Extensive blood studies showed the following abnormalities: bromsulphalein retention 38% in 45 minutes, serum alkaline phosphatase 180 IU, SGOT 142 IU, prothrombin time 15.2 (control 11.4), serum albumin 2.4 g/dl. Scintiscans showed enlargement of the liver and spleen, and diminished and inhomogeneous hepatic uptake of radiocolloid. Barium contrast upper gastrointestinal x-rays were normal. Angiographic studies were not repeated.

A side-to-side portacaval shunt was performed nine weeks after the onset of symptoms. The findings at operation were 8.7 l of ascites, marked enlargement and congestion of the liver, splenomegaly and the following pressures in mm saline: IVCP 112; FPP 342; HOPP 338; SOPP 348. Post-shunt pressures were: IVCP 168; FPP 176. A liver biopsy showed intense congestion and necrosis around the central veins and moderate fibrosis.

The postoperative course was complicated by transient jaundice and transient reaccumulation of ascites which responded to diuretic therapy. The patient was discharged from the hospital 22 days after the shunt procedure and by four months postoperatively had resumed normal activity and employment, at which time he had gained 36 pounds in lean body weight. During three years of follow-up he remained free of ascites without diuretic therapy, and periodic tests of liver function showed normal results. There has been no evidence of portal-systemic encephalopathy. A follow-up needle liver biopsy performed three years postoperatively showed moderate fibrosis, but no other abnormalities. Angiographic studies performed after three years failed to visualize the occluded hepatic veins but showed a widely patent protacaval shunt and IVC with pressures that measured 144 mm. saline in the IVC and 158 mm saline in the PV.

Case 5. This 19-year-old white male was admitted to another hospital with a two week history of progressive abdominal distention, diffuse upper abdominal pain, weakness, anorexia and recent fever of 101°F. He had been in excellent health prior to the onset of symptoms and past history was non-contributory. He was found to have ascites, hepatomegaly and mildly disturbed liver function. Scintiscans showed diffuse mottling of the liver and an enlarged spleen. Angiographic studies showed a normal IVC and PV, and stretching of the hepatic artery branches within the liver. A laparotomy was performed for open liver biopsy and showed massive ascites and an enlarged, congested liver. The liver biopsy demonstrated intense centrilobular congestion and necrosis compatible with the diagnosis of Budd-Chiari syndrome. A Foley catheter drain was left in the peritoneal cavity and subsequently drained large quantities of ascitic fluid. The patient was transferred to University Hospital three weeks after the onset of symptoms.

On admission to our institution the positive physical findings were evidence of moderate muscle wasting, hepatomegaly and a distended abdomen draining copious amounts of ascites. The patient appeared acutely ill. There was no jaundice or peripheral edema. Bacterial cultures of the ascitic fluid showed a heavy growth of S. aureus and Klebsiella indicating that the ascites had become infected, and appropriate therapy was instituted. The only abnormal results of extensive blood studies were: bromsulphalein retention 23% in 45 minutes, serum alkaline phosphatase 170 IU, and serum albumin 2.5 g/dl. Scintiscans showed enlargement of the liver and spleen and inhomogeneous uptake of radiocolloid in the liver. Barium contrast upper gastrointestinal x-rays were normal. A second set of angiographic studies showed a patent IVC with side-to-side compression of the intrahepatic segment by an enlarged liver, occlusion of the hepatic veins with formation of spider-like webs of vessels, stretching and attenuation of the intrahepatic branches of the hepatic artery, and a normal PV. IVCP was 126 mm saline. A diagnosis of Budd-Chiari syndrome with thrombosis of the hepatic veins of unknown etiology was made.

A side-to-side portacaval shunt was performed on the seventh day of hospitalization, four weeks after the onset of symptoms. The findings at operation were an enlarged, congested liver covered by stringy adhesions, splenomegaly, six l of ascites (cultures of which grew S. aureus), and the following pressures in mm saline: IVCP 120; FPP 265; HOPP 200; SOPP 305. After construction of the portacaval shunt pressures were: IVCP 175; FPP 165. A liver biopsy showed the microscopic lesions characteristic of Budd-Chiari syndrome, namely, marked centrilobular congestion and necrosis and a modest increase in fibrous tissue.

The postoperative course was complicated by transient reaccumulation of ascites which responded to diuretic therapy, a minor wound infection, low grade fever and leucocytosis which responded to antibiotic therapy. The patient was discharged three weeks postoperatively. However, he was readmitted to the hospital one month later because of persistent low grade fever and the demonstration of a large fluid collection in the pelvis by ultrasonography which proved to be an abscess caused by S. aureus, the same organism that was identified in the infected ascitic fluid at the time of his initial admission. Drainage of the pelvic abscess resulted in prompt recovery. When last seen eight months postoperatively the patient was free of ascites, had gained 40 pounds in lean body weight, had a normal sized liver and spleen, had normal liver function and was working full-time. There has been no evidence of portal-systemic encephalopathy.

Case 6. This 28-year-old previously healthy white male was admitted to another hospital with a two month history of progressive increase in abdominal girth, diffuse abdominal pain, fatigue and anorexia. He was found to have massive ascites, marked hepatomegaly and mild jaundice. There was no peripheral edema. Laboratory studies showed erythrocytosis, an increased blood volume, a normal plasma volume and hyperplastic bone marrow compatible with the diagnosis of polycythemia rubra vera. Liver function tests showed a total serum bilirubin of 2.7 mg/dl, serum alkaline phosphatase of 140 IU and SGOT of 177 IU. A liver scintiscan showed diffusely mottled uptake of radiocolloid. Barium contrast upper gastrointestinal x-rays were normal. The patient was treated for three weeks with phlebotomy and diuretics, but his ascites progressed, his liver function deteriorated and he grew weaker. Angiographic studies were then performed and showed a normal inferior vena cava and portal vein, and thrombotic occlusion of all of the hepatic veins with reversal of flow into the portal vein. A diagnosis of Budd-Chiari syndrome was made and the patient was transferred to University Hospital three months after the onset of symptoms.

On admission to our institution the patient had mild jaundice, marked hepatomegaly, tense ascites and evidence of severe muscle wasting and loss of lean body mass. There was no peripheral edema. Extensive hematologic studies confirmed the suspicion of polycythemia rubra vera. The results of all liver function tests were abnormal and included: prothrombin time 16.5 seconds (control 11.9 seconds), partial thromboplastin time 41.5 seconds (control 37.9 seconds), serum bilirubin 3.9 mg/dl, bromsulphalein retention 90 per cent in 45 minutes, SGOT 540 IU and serum alkaline phosphatase 345 IU. Scintiscans showed hepatosplenomegaly and abnormal uptake of radiocolloid similar to that demonstrated previously.

The patient was treated with phlebotomy and diuretics as his diagnostic workup progressed. On the evening of the eighth day of hospitalization his condition deteriorated and he developed edema of the lower extremities and lower trunk. In addition, he developed an infiltrate in the left lower lung and a left pleural effusion which raised the consideration of pulmonary embolus. Angiographic studies were repeated the next day and demonstrated extension of the thrombotic process to involve the previously patent abdominal IVC and both iliac veins (Fig. 6). Pressures in the IVC were 20 mm saline at a level above the diaphragm and 300 mm. saline at the level of entrance of the renal veins. Following the angiographic studies, edema of the lower extremities and trunk progressed rapidly, oliguria developed and blood studies showed a urea nitrogen of 47 mg/dl and creatinine of 3.1 mg/dl.

An emergency side-to-side portacaval shunt and IVC thrombectomy was undertaken. The findings at operation were 15.9 l of ascites, a large congested liver, thrombosis of the entire abdominal inferior vena cava, and the following pressures in mm saline: IVCP 250; FPP 434; HOPP 486; SOPP 422. Following the portacaval shunt the pressures were: IVCP 284; FPP 284.

The patient died six days postoperatively with reaccumulation of ascites, hepatic failure, renal failure, respiratory failure and gastrointestinal bleeding. Autopsy findings included thrombosis of the hepatic veins and entire inferior vena cava, and an embolus in the left main pulmonary artery. Microscopic sections of the liver showed severe centrilobular congestion and loss of parenchyma.

Discussion

In many if not most patients with Budd-Chiari syndrome due to occlusion of the hepatic veins, the diagnosis has not been made until the autopsy was done or the patient was near death. Nevertheless, with available diagnostic techniques it should be possible in most cases to identify the condition early in its course. The clinical picture of ascites, hepatomegaly, abdominal pain and disturbed liver function, often occurring in a patient who is below the age of 50 years and previously has been in good health, should strongly suggest the diagnosis. Most acute hepatic diseases, particularly the common ones, do not produce ascites as an early manifestation. The most valuable diagnostic study is angiography of the IVC and hepatic veins with pressure measurements. Demonstration of a patent IVC (sometimes compressed in its intrahepatic course by the swollen liver), normal or only moderately elevated IVC pressure (due to massive ascites), and occlusion of the major hepatic veins often with a spider web pattern of small collateral vessels is diagnostic of Budd-Chiari syndrome, particularly in the presence of appropriate clinical manifestations.[13,28,49,58] All six patients described in this report had these clinical and angiographic findings. An elevated wedged hepatic vein pressure strengthens the diagnosis when this measurement can be obtained, although it is not an essential procedure.

Although the diagnosis can be made with assurance in the absence of a liver biopsy, microscopic examination of the liver is another diagnostic procedure of definitive value. The findings of intense centrilobular congestion and centrilobular necrosis or loss of parenchyma in the face of a normal or only moderately elevated IVC pressure indicates hepatic venous outflow obstruction. This typical picture was observed in the liver biopsies obtained from all six of our patients, including the three who underwent preoperative biopsies.

Hepatic scintigraphy has been reported to be of value as a screening procedure in patients with the Budd-Chiari syndrome.[36,58] In addition to decreased and inhomogeneous hepatic uptake of radiocolloid, the finding of central localization of radiocolloid due to uptake by an enlarged and unobstructed caudate lobe which is drained directly into the IVC by small hepatic veins, has been reported to be of diagnostic significance.[36,58] This phenomenon was observed in only two of our six patients, so that liver scanning was not of great value in our experience.

Treatment of the Budd-Chiari syndrome by side-to-side portacaval shunt, or other shunts that are hemodynamically equivalent, is based on sound experimental and clinical evidence. The side-to-side shunt decompresses the obstructed hepatic vascular bed by both diverting the inflow of splanchnic venous blood and allowing retrograde egress of hepatic blood through the portal vein into the low pressure vena cava. Many studies have conclusively demonstrated that side-to-side shunt converts the valveless portal vein into an outflow tract. Animal experiments have shown that in the presence of a side-to-side shunt or its equivalent it is possible to acutely occlude hepatic venous outflow.[12,14,15] Moreover, reversal of flow in the portal vein has been documented in both animals and humans with side-to-side portacaval shunts by direct flow measurements, dye and radioisotope studies, and angiography.[6,7,10,31,32,37–39,41,57,61] Furthermore, pressure measurements in cirrhotic patients with side-to-side portacaval shunts have consistently shown a marked reduction of hepatic sinusoidal pressure, often to the normal level.[50,61]

The results of our experimental studies in dogs with Budd-Chiari syndrome produced by ligation of the hepatic veins demonstrated clearly that side-to-side portacaval shunt was very effective in relieving ascites, hepatomegaly, hepatic congestion and portal hypertension. Only one of 24 animals, 18 of which were long-term survivors, reformed ascites after side-to-side anastomosis, and 67% of the dogs were alive and well when the study was concluded after one year. Moreover, liver biopsies showed that side-to-side shunt eliminated the congestion and necrosis that are characteristic of hepatic outflow occlusion, and in one-third of the dogs caused reversion of the morphologic picture to normal. In contrast, all control dogs that were subjected to sham laparotomy and all dogs that underwent end-to-side portacaval shunt reformed massive ascites and died within six months with continued hepatic congestion and necrosis, despite the fact that the end-to-side anastomosis reduced the splanchnic portal pressure to normal. In clinical studies in cirrhotic patients, end-to-side portacaval shunt has not been as effective as side-to-side shunt in reducing sinusoidal hypertension, and high sinusoidal pressures have persisted in some patients.[22,29,59]

Successful treatments of the Budd-Chiari syndrome due to occlusion of the hepatic veins by side-by-side portacaval shunt, splenorenal shunt or mesocaval H-graft has been accomplished in at least nine patients reported by eight authors.[4,5,18–20,30,35,40,48,54] Interestingly, all of the patients were relatively young women ranging in age from 18 to 43 years. The underlying condition was polycythemia vera in three, leukemia in one, ingestion of oral contraceptives in one and unknown in four. Long-term follow-up results from three to eight years postoperatively have been reported in five of these patients. All of them have remained free of ascites. Blakemore's patient, the first reported,[4] died of leukemia eight years after operation.[5] The patient described by Eisenmenger and Nickel[18] died of a cerebral hemorrhage three years postoperatively.[5] The patient reported by Erlik and associates[19] died of a brain abscess after five years of normal life.[54] The patient of McAllister and Barker,[35] reported by Britton et al.,[5] was alive five years postoperatively, and the patient of Langer and his colleagues[30] was living and well four years after portacaval shunt. None of the deaths were related to liver disease. In only one of these patients, that of Erlik et al., was the liver examined microscopically after several years had elapsed, and the findings consisted of continued sinusoidal congestion but no fibrosis.[54] Little is known about the long-term effects on hepatic morphology of hepatic vein occlusion that has been treated by side-to-side portacaval shunt.

In at least 11 patients with Budd-Chiari syndrome reported by nine authors,[3,5,17,19,21,26,30,33,34,54] treatment by side-to-side portacaval shunt or splenorenal shunt failed and the patient died. In seven of these patients, the shunts were a technical failure and developed thrombosis or did not adequately decompress the portal system because of small size.[3,17,19,21,26,34] In one patient, the shunt was performed in the face of thrombosis of the IVC, an inappropriate undertaking.[33] Three patients were operated upon while in coma, shock or renal failure.[30,54] From the case descriptions it appears that for one reason or another all 11 of these failures were characterized by an unsatisfactory operation and/or an unsuitable patient.

The results of side-to-side portacaval shunt in our small series of six patients with Budd-Chiari syndrome due to hepatic vein thrombosis, confirmed our experimental observations regarding the efficacy of this procedure in relieving hepatic venous outflow obstruction. All five patients in whom thrombosis was confined to the hepatic veins survived the operation and remained free of ascites without requiring diuretic therapy during follow-up periods of from eight months to seven years. Hepatosplenomegaly disappeared and liver function returned rapidly to normal and has remained so. The shunt operation was followed by a rapid gain of lean body weight and return of vigor. In contrast to the 26% incidence of portal-systemic encephalopathy in our large series of alcoholic cirrhotics with portacaval shunts,[44] none of the patients have developed encephalopathy or required dietary protein restriction. Angiographic studies performed from three to six years after operation in four patients showed a patent IVC, a widely patent portacaval anastomosis, and persistent occlusion of the hepatic veins with no evidence of recanalization. The results of liver biopsies obtained from three to six years postoperatively in four patients were particularly encouraging. They showed mild to moderate fibrosis, but no congestion or necrosis. Long-term evaluation of hepatic morphology will be of particular importance in this relatively young group of patients.

One patient in our series died, and this case deserves comment. When this 28-year-old man with polycythemia vera was admitted to our hospital there was clear clinical and angiographic evidence that the occlusive process was confined to the hepatic veins. However, during the eight-day course of his diagnostic work-up the thrombosis extended into the IVC and his condition deteriorated dramatically. Not surprisingly, an emergency attempt at vena cava thrombectomy and portacaval shunt failed. There are several potentially valuable lessons to be learned from this experience. Firstly, extension of the thrombotic process from the hepatic veins into the IVC is a well known event in the Budd-Chiari syndrome[46] and the potential for this devastating complication exists in every patient. Whether or not a portacaval shunt will prevent such extension remains to be determined by further experience, but it seems plausible to suggest that the increased blood flow in the IVC and the relief of stasis in the liver resulting from the shunt will have an antithrombosis effect. Secondly, it is important to emphasize that obstruction or occlusion of the IVC, manifested clinically by edema of the lower extremities and lower trunk and demonstrable by angiography and IVC pressure measurements, is a contraindication to portacaval shunt. Thirdly, once the diagnosis of hepatic vein occlusion has been made, it would seem unwise to delay operation. Although an occasional patient has recovered spontaneously, the overwhelming majority have not. The literature contains numerous descriptions of patients who would have been suitable candidates for portacaval shunt, but were treated nonoperatively and died. A case described by Schramek and his associates[54] is one of many that illustrate this point. A clear-cut diagnosis of Budd-Chiari syndrome due to hepatic vein occlusion was made in a 41-year-old woman. A decision was made to treat the patient nonoperatively and the report indicates that one year later the patient was doing well. However, an addendum to the report indicates that two years after the diagnosis was made, the patient was admitted to the hospital in coma with massive upper gastrointestinal bleeding (from esophageal varices) and died shortly after an attempt was made at emergency portacaval shunt.

Mention should be made of some unique forms of the Budd-Chiari syndrome, if only to emphasize that they are not suitable for treatment by side-to-side portacaval shunt and, therefore, must be ruled out by the diagnostic work-up. Membranous obstruction of the IVC just below the diaphragm has been reported sporadically from various countries around the world, including the United States, but almost all of the more than 100 cases have been reported from Japan.[16,24,27,51,63] This condition usually runs a course of many years, and a congenital etiology has been proposed. We have not encountered a case of IVC membrane or web in our 25 years of experience with a sizeable population of ascitic patients. The disorder has been treated successfully by transcardiac membranotomy, direct excision of the membrane, or bypass grafting. Some authors have included the veno-occlusive disease caused by ingestion of pyrrolizidine alkaloids,[8,55] and the peculiar veno-occlusive disease observed in children in the Near East.[1,23,53] However, the occlusive process in these chronic disorders is located mainly or entirely in the small hepatic venules within the liver so that their membership in the Budd-Chiari syndrome is questionable.

Since the time when the Budd-Chiari syndrome due to occlusion of the hepatic veins was first well described some eight decades ago, the record of treatment of this condition has been dismal and the mortality rate has been very high. The results of our experimental studies combined with our small but consistent clinical experience indicate that side-to-side portacaval shunt provides definitive treatment of hepatic vein occlusion and offers the possibility of long-term survival. Early diagnosis and prompt operation appear to be important ingredients of the therapeutic regimen.

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DISCUSSION

DR. ARTHUR B. VOORHEES, JR. (New York, New York): There seems to be, in our clinical experience, at least, in New York, two basic forms. There is what one would describe as an acute form, which is fulminating, it's rarely diagnosed anteoperatively, and most often the diagnosis is made at the post-mortem examination. It is characterized by a relatively fresh clot involving most of the hepatic outflow tract.

In the perhaps six instances that we have faced in this category, we have been able to achieve a side-to-side shunt only in one, and that was unsuccessfull in so far as patient survival is concerned.

Although at this point I draw from memory of some 2000 patients that have presented in our institution with evidence of portal hypertension, the anteoperative and the intraoperative diagnosis has been made only in three instances, where we consider this to be of a more chronic nature, as we have just heard described by Dr. Orloff.

In the three instances that I speak of, a side-to-side shunt was first achieved by Arthur Blakemore in 1948, and has been subsequently repeated on two occasions, bringing our experience to a total of three. Two of these have survived.

In brief, I agree with Dr. Orloff that when the hepatic outflow tract has been obstructed, a side-to-side portacaval shunt can be a life saving and a precisely designed therapeutic procedure.

Finally, I'd like to offer a brief word of caution, which Dr. Orloff has already described in part, but I would like to expand upon it very briefly. That is a so-called functional Budd-Chiari syndrome, originally described by Professor Fraga, of the University of Brazil. It is produced primarily by a retrohepatic vena caval narrowing, and as in Dr. Orloff's instance, where the vena cava was obstructed by clot, a side-to-side shunt in this particular instance of vena caval narrowing, due primarily to cirrhosis, of course, is ineffective.

I think it should be emphasized that Dr. Orloff has drawn our attention to a very rare problem—in our experience, approximately 0.5% in our overall group of hypertensives.

I'd like to just close my remarks by stating that I'd like to have Dr. Orloff present, perhaps, in the next few years some detailed studies of the survivors.

DR. WILLIAM V. MCDERMOTT, JR. (Boston, Massachusetts): This excellent paper is an example of Marshall Orloff's presenting to us another of his continuing excellent clinical and experimental studies on the pathogenesis and treatment of ascites, this time based on a series of six cases of the so-called Budd-Chiari syndrome, an unusual cause of postsinusoidal block.

Basically, the pathophysiology involved in the formation of this type of ascites is similar, regardless of whether the outflow block is located in the suprahepatic or retrohepatic vena cava, the major hepatic veins, the intrahepatic small venules, (as in "bush tea" or Senechio poisoning), or is due to the changes secondary to cirrhosis, all of which involve obstruction to outflow from the central veins of the hepatic lobule.

Obviously, the first of these, an occluding diaphragm, in the suprahepatic vena cava, presents a separate problem. It's more common in the Orient than in this country. It can be, treated appropriately by transatrial fracture.

The other three causes, if nearly complete and unmanageable by medical therapy, do require the re-establishment of an outflow tract. This may occur spontaneously, but slowly, through the development of reversal of flow in the portal vein, (as in the case of the Cruveilhier-Baumgarten syndrome) or more rapidly and effectively by surgical construction of any one of the shunts which do provide combined hepatic and portal decompression. That means side-to-side, double, portacaval, interposition mesocaval shunts, etc. It's very effective in reversing the multiple metabolic and nutritional disorders.

In the era before the medical management of cirrhotic ascites was very effective, a number of reports from our unit, from Welch, Longmire and others, were concerned with this problem. As one example, I'd like to show you three slides.

(Slide) This was one of the types (a double portacal shunt) of combined decompression which provides a reversal of flow from the congested intrahepatic circulation.

(Slide) This is one of the patients who, despite—or perhaps you could say, because of four months on the medical wards—was in this terrible state of marasmus, with completely intractable ascites.

(Slide) Four months after a combined decompression, she not only lost her ascites, but most impressively, had regained an excellent state of nutrition.

In terms of long-term follow-up, this young woman eventually drank herself to death about nine years postoperatively, but never during that period of time, despite repeated bouts of so-called alcoholic hepatitis and jaundice, did she ever re-establish ascites, nor did she develop encephalopathy.

(Slide) Metabolically, the reversal occurs very rapidly, as you can see in this slide on the balance studies, particularly in terms of sodium metabolism. Characteristically, 0–3 or 5 mM/l is the level of urinary loss with an increased excretion of potassium; but within a very few days of operation, you can see the remarkable reversal in the pattern of electrolyte balance, with the re-establishment of a normal sodium/potassium ratio on a completely unrestricted salt intake.

So, decompression works very rapidly in correcting this abnormality.

Now, this particular sequence was concerned with the severe degree of postsinusoidal block one may encounter with cirrhosis—but we have seen the same syndrome with "bush tea" Senechio poisoning, a peculiar process of obliteration of the smaller hepatic venules, by Professor Brass, of the University of the West Indies, to the ingestion of toxic alkaloids in herbal teas brewed by the natives in the Jamaican highlands.

This particular case also reverted to normal after a similar type of combined decompression.

The cases of occlusion of the major hepatic veins, as described by Dr. Orloff, may well require surgical construction of an outflow tract via the portal vein. I do want to point out that these may recover spontaneously, as we have seen in two instances—young women in whom the Budd-Chiari syndrome was apparently related to the ingestion of oral contraceptives; both of them, on conservative management, appeared to re-establish an adequate collateral outflow, so the syndrome slowly reversed without the necessity of a shunt.

I would agree, however, that this does not occur regularly or predictably, and therefore it is well to keep in mind the principles which Dr. Orloff has expressed today.

There is one particular facet of this problem that I think is of particular interest, which is the absence of encephalopathy in this series, and in our own experience. With this particular syndrome and with decompression by a combined shunt of any of these varieties, we have never encountered a case of postshunt encephalopathy.

In the manuscript, Dr. Orloff has suggested that this may be related to the lack of hepatocellular disease; but it is the organism, man or experimental animal, with no disease of the liver or portal circulation who is most prone to the development of this syndrome after the construction of a shunt.

For some years we have wondered how the presence of a postsinusoidal block might alter the intrahepatic hemodynamics and perhaps permit a type of perfusion of the hepatic cell by the hepatic arterial inflow which differs from in the shunts which we do for the common types of intrahepatic block. I would like to ask Dr. Orloff if he has any further thoughts on this.

DR. WILLIAM P. LONGMIRE, JR. (Los Angeles, California): I rise to make a few comments on Dr. Orloff's elegant experimental studies and his very complete clinical evaluation of these six patients.

We have had occasion over the past few years to see three patients who presented some problems pertinent to this discussion. One was a 19-year-old lad who during a three-month period had developed an extensive incapacitating ascites. While considering the care of this patient, the literature on this subject was reviewed, and as Dr. Orloff states in his paper, the majority of reports dealing with surgical correction of this disease point to the inadequacies of side-to-side anastomosis. As he has also indicated, however, many of the poor results may be attributable to technical error.

In any event, it was impossible for us to convince our medical colleagues that a portacaval shunt would benefit this young man, and we continued to observe him for a period of approximately 2.5 months when his ascites began spontaneously to regress and eventually disappeared completely. He returned to a normal state and has remained so for almost a year.

On the other hand, as Dr. Orloff discussed in his paper, spontaneous improvement has been described only to be followed by subsequent recurrence of ascites. We will be interested in following our patient to see if he remains well or if the condition causing his original ascites returns.

Our other two patients presented with obstruction in the inferior vena cava in addition to hepatic vein obstruction. The caval obstruction in the first patient was well-localized to the region of the entrance of the hepatic vein; Dr. Donald Mulder was able to bypass successfully the blockage of the inferior vena cava and hepatic veins with a vascular graft between the portal vein and the right atrium.

Our third patient was one quite similar to Patient No. 6 in Dr. Orloff's series, with extensive thrombosis in the inferior vena cava, who arrived in our institution in a terminal condition and expired shortly thereafter.

This series of Budd-Chiari patients represents the largest I know of treated surgically with such successful results, and these results will provide a guide for the surgical management of future patients.

I am still somewhat worried about the spontaneous improvement of patients like those Dr. McDermott and I have described. This phenomenon raises a question as to how often this improvement may occur and how permanent the improvement may be. I would like to ask Dr. Orloff to comment further regarding this problem.

DR. HARRY H. LAVEEN: The fact that Dr. Orloff had only one death in six patients proves only that Dr. Orloff can do side-to-side shunts better than most of us. However, he has offered no evidence that this is the correct procedure to use.

(Slide) In 1974 a technique for doing peritoneojugular shunt was described to this society, and that technique was worked out and perfected on dogs with Budd-Chiari syndrome.

During the discussion, a young surgeon from Oregon named Larry Idemore recounted to us a most extraordinary case, and I should like to repeat his brief words:

We recently encountered an unusual case of Budd-Chiari syndrome in a 34-year-old man who was explored at another hospital for weight loss, fatigue, epigastric pain, and jaundice. At laparotomy he was found to have 200–300 cc of slightly bloody ascitic fluid, portal venous hypertension and a swollen, turgid liver and spleen. Liver biopsy showed canalicular stasis and venous congestion.

Postoperatively, he did very poorly, and was transferred to the University of Oregon Hospital with progressive ascites and hepatorenal failure. A cavagram revealed a thrombosis of the hepatic veins and the intrahepatic vena cava. Visceral angiography confirmed the presence of portal hypertension, and also disclosed portal and splenic vein thrombosis.

By this time the patient was deteriorating rapidly with massive ascites, requiring daily paracenteses for respiratory failure. His hepatorenal failure and moribund state made him a very poor candidate for any kind of surgery. However, a peritoneal-venous shunt was placed under local anesthesia. There was a prompt recovery in hepatic and renal function after placement of the shunt.

(Slide) This does not really demonstrate to you the dramatic clinical improvement which occurred in this patient. He was discharged at 14 days, ascites free, and is now five months after operation; he has nearly normal liver function.

In 1976, in a paper on ascites, we recounted eight cases of Budd-Chiari syndrome, and Dr. Liebowitz offered a case history of a ninth to us. Since that time, surgeons throughout the United States have made me aware of a total of 18 cases that have been treated by peritoneojugular shunt. One patient had a necrotic bowel and peritonitis, and was not treatable by this method. All of the other 17 cases were commonplace, ordinary successes.

Dr. Orloff tells us that a side-to-side shunt may be the procedure to do on these patients; but this is a procedure that has quite an unphysiologic result in the long term, and I think the simpler peritoneojugular shunt is a better alternative.

The peritoneojugular shunt is a prospective operation, proved by randomly selected double-blind surgeons and Sunday morning surgeons, but with a rather good success rate. The fact that the 17 patients all recovered is even more striking. I would suggest to you that the simpler peritoneojugular shunt be the procedure of choice.

DR. JOHN CAMERON (Baltimore, Maryland): I would like to line up behind Dr. Orloff, suggesting that some kind of portal-systemic decompression is necessary for the long-term survival of most patients with the Budd-Chiari syndrome. I think the natural history of the disease has been well demonstrated over the past 50 years, and although all patients don't die within a month or two, 90% of them will die within one to two years after the diagnosis is made.

We have taken a somewhat different approach in achieving portal decompression (slide) and have used the superior mesenteric vein to decompress the portal system in all patients. We've managed four patients surgically in the last three years. The portion of the superior mesenteric vein on top of the third portion of the duodenum in the uncinate process, just before it enters posteriorly behind the neck of the pancreas, has been used. In the majority of patients with the Budd-Chiari syndrome the inferior vena cava is patent, and a mesocaval shunt can be performed. Using the cephalad portion of the superior mesenteric vein allows one to perform the anastomosis in a portion of the vein where it is always quite large and before it branched. This gives one a C-configuration to the mesocaval shunt, rather than the H-configuration.

However, the patients that are the most difficult to manage are not those with a patent inferior vena cava and with a low pressure in the cava, but those patients in whom the inferior vena cava is thrombosed, of whom there are considerable numbers. In addition, some patients have markedly elevated inferior vena caval pressures, secondary to a hypertrophied caudate lobe. In these patients a portaseptemic decompression to the inferior vena cava cannot be carried out.

(Slide) This is the inferior vena cavagram of a patient whose inferior vena cava was involved in the thrombotic process that involved her hepatic veins. This demonstrates collaterals in the retroperitoneum. This patient also had the superior mesenteric vein used as the outflow tract, but instead of a short 6- or 8-cm segment of Dacron graft anastomosed to the inferior vena cava, a 20 cm segment was used. After the anastomosis was performed end-to-side to the superior mesenteric vein, the graft was passed through the transverse mesocolon, on top of the stomach and into the mediastinum just below the xiphoid. Once into the anterior mediastinum, it was brought out into the right chest and an anastomosis made end-to-side to the right atrium.

This patient is now a year-and-a-half post-mesoatrial shunt, is asymptomatic, without ascites, is employed and has no difficulties with encephalopathy, as do any of our other patients treated for the Budd-Chiari syndrome.

(Slide) This is a superior mesenteric arteriogram obtained postoperatively. You can see the superior mesenteric vein well visualized. The graft, which is not quite as long as you might expect for a mesoatrial shunt, empties in the right atrium. The flow is so rapid that one can actually see the right atrium well outlined with contrast media.

In summary, I think the Budd-Chiari syndrome is a disease that is surgically manageable, if not curable, even in the face of a thrombosed vena cava, or in an instance where the pressure in the inferior vena cava is so high that it's not an acceptable receptacle for a portal systemic decompression. The Budd-Chiari syndrome is certainly manageable without hepatic transplantation, as others have suggested.

I would like to ask Dr. Orloff what the advantages of a side-to-side portacaval shunt are over a mesocaval shunt. We have felt that, particularly in the face of a markedly congested and enlarged liver with the Budd-Chiari syndrome, technically it's been much easier to do a mesocaval shunt, particularly with the C-configuration. In the world literature it's our impression that the patency rate, along with the ease of construction, is at least as satisfactory with the mesocaval as the side-to-side portacaval.

DR. MARSHALL J. ORLOFF (Closing discussion): I wish to thank Drs. Voorhees, McDermott, Longmire, LaVeen and Cameron for their interesting and penetrating comments. No one has had extensive experience with the Budd-Chiari syndrome due to hepatic vein occlusion, and even though our six patients treated by side-to-side shunt represent the largest single experience reported to date, I can hardly claim that six cases constitute a large experience. As the discussants have emphasized, the Budd-Chiari syndrome is an uncommon condition.

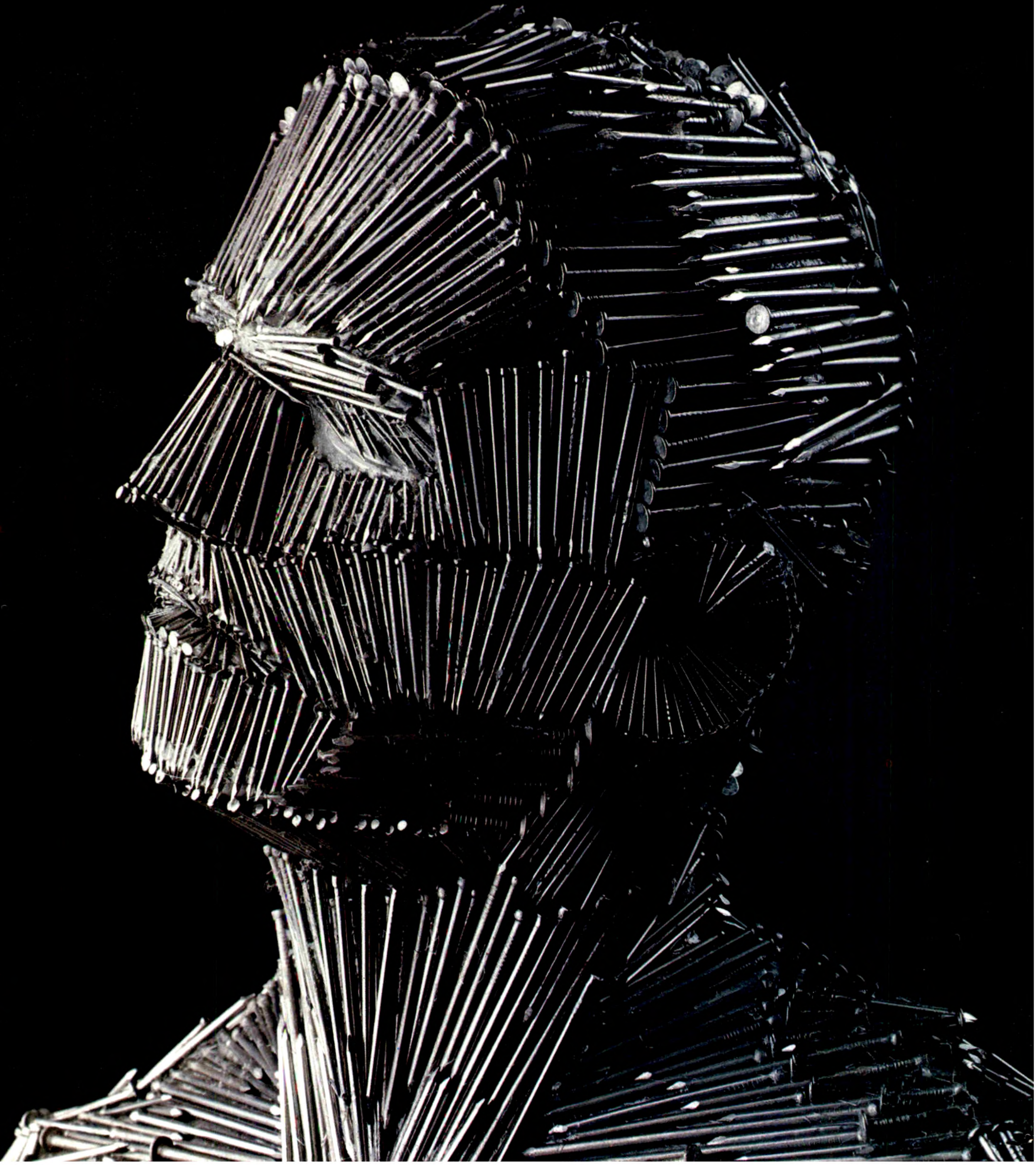
I would like to make two generic comments that may answer several of the questions. The first comment is that the Budd-Chiari syndrome due to hepatic vein occlusion is fatal in 90–95% of the cases. I cannot make that statement on the basis of our own small experience, but we have reviewed the literature thoroughly and it is clear that the overwhelming majority of reported patients have died. Spontaneous recovery has been reported and undoubtedly occurs, but it must be rare. The patient described by Dr. Longmire, who appears to have recovered spontaneously for one year since the onset of the condition, is reminiscent of several cases reported in the literature, such as the case described by Schramek et al. from Israel. In a 1974 paper in Annals of Surgery, Schramek et al. described a patient who was alive and well one year after a deliberate decision was made to treat the Budd-Chiari syndrome nonoperatively. However, in an addendum to the report, sent in after the manuscript was accepted, Schramek et al. indicated that two years after the onset of the disease the patient entered the hospital in coma with bleeding esophageal varices and died during an attempt at emergency portacaval shunt. I am hopeful that this will not happen to Dr. Longmire's patient, but the syndrome is known to wax and wane and ultimately to result in the death of most patients. It is for this reason that we advocate an aggressive diagnostic and therapeutic approach, with early portacaval shunt.

The second generic comment concerns the type of shunt. Theoretically, any shunt that embodies the side-to-side shunt principle will effectively decompress the liver, and that includes direct side-to-side portacaval anastomosis, mesocaval shunt, mesocaval H-graft, mesorenal shunt and even the conventional splenorenal shunt. All of these shunts convert the portal vein into an outflow tract by an in-continuity anastomosis between the portal system and the systemic circulation. Dr. Longmire and his associates were among the first to show that side-to-side portacaval shunt converts the portal vein into an outflow tract and, since then, numerous investigators have confirmed this observation. A fundamental principle of shunt therapy for Budd-Chiari syndrome is replacement of the occluded hepatic veins with a new outflow tract, namely, the portal vein. Time does not permit a discussion of which type of in-continuity shunt is best, but it is clear that an in-continuity shunt is needed.

Regarding Dr. LaVeen's comments, I cannot comment from personal experience on the effectiveness of the LaVeen shunt in Budd-Chiari syndrome since my only experience with this device has been in removing it from a sizable number of patients with cirrhotic ascites who had it inserted by other surgeons and were then sent to us because of complications or nonfunction. However, I must take strong exception to several of his comments. Firstly, the dog experiments which he claimed demonstrated effectiveness of the LaVeen shunt in Budd-Chiari syndrome did not involve animals with hepatic vein occlusion. Rather, they involved constriction of the IVC, which is quite different from the condition that is the subject of our report. Secondly, his reference to 17 patients that have been "cured" of the Budd-Chiari syndrome by the LaVeen shunt is purely anecdotal and is similar to much of the other information that has been reported on the LaVeen shunt. If indeed, the peritoneojugular shunt is effective in the Budd-Chiari syndrome, then he should prove it by a systematic study of patients with this condition, diagnosed by accepted criteria and then subjected to long-term follow-up with liver biopsies and measurements of liver function as we have done in our study. I doubt that he can provide such information at the present time. I have to say, on the basis of the principles involved, that I doubt that the LaVeen shunt, which simply returns ascites from the peritoneal cavity to the jugular vein, will be effective in the Budd-Chiari syndrome due to hepatic vein occlusion. The peritoneojugular shunt has no effect on the fundamental problem, which is intense congestion and necrosis of the liver that ultimately leads to death from liver failure or from the complications of portal hypertension, such as bleeding esophageal varices. It is not the ascites that kills patients with Budd-Chiari syndrome, but the intense congestion of the liver. Dr. LaVeen's comments suggest that he does not understand the Budd-Chiari syndrome.

Finally, regarding Dr. Cameron's question I cannot comment on the treatment of IVC occlusion on the basis of experience. The ingenious operation that he mentioned, namely a bypass graft between the superior mesenteric vein and the right atrium, has been reported to be successful on occasion, although most attempts at treating IVC thrombosis have failed. Similarly, success has been reported, particularly from Japan, in treating IVC webs and membranes by finger fracture, direct excision and bypass grafts between the lower IVC and the right atrium. I can only emphasize that the natural history and treatment of Budd-Chiari syndrome due to IVC obstruction is quite different from Budd-Chiari syndrome due to hepatic occlusion, and that the two entities must be considered separately.

In search of
Victory over pain



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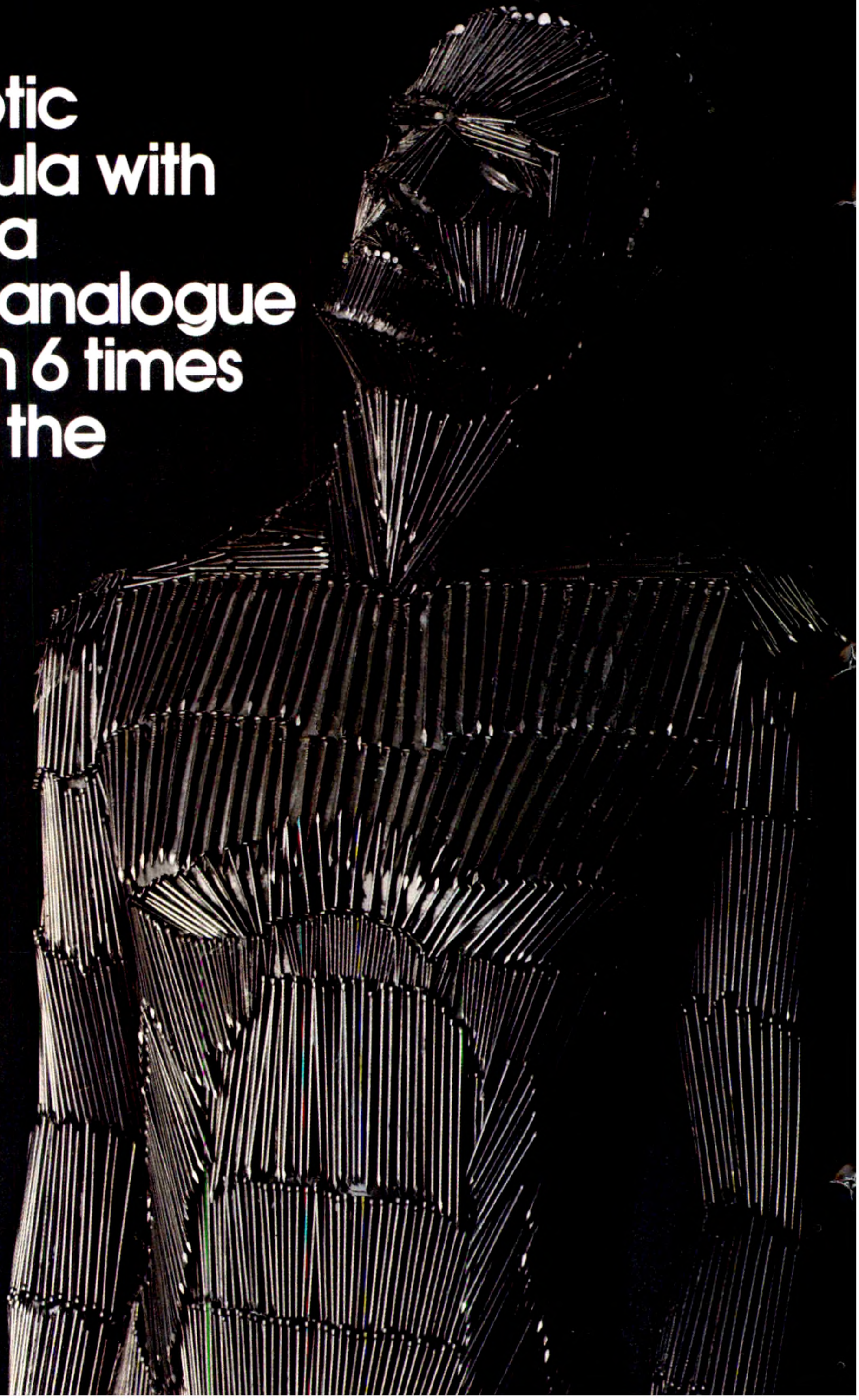


A unique narcotic analgesic formula with hydrocodone–a semi-synthetic analogue of codeine with 6 times the potency of the parent drug

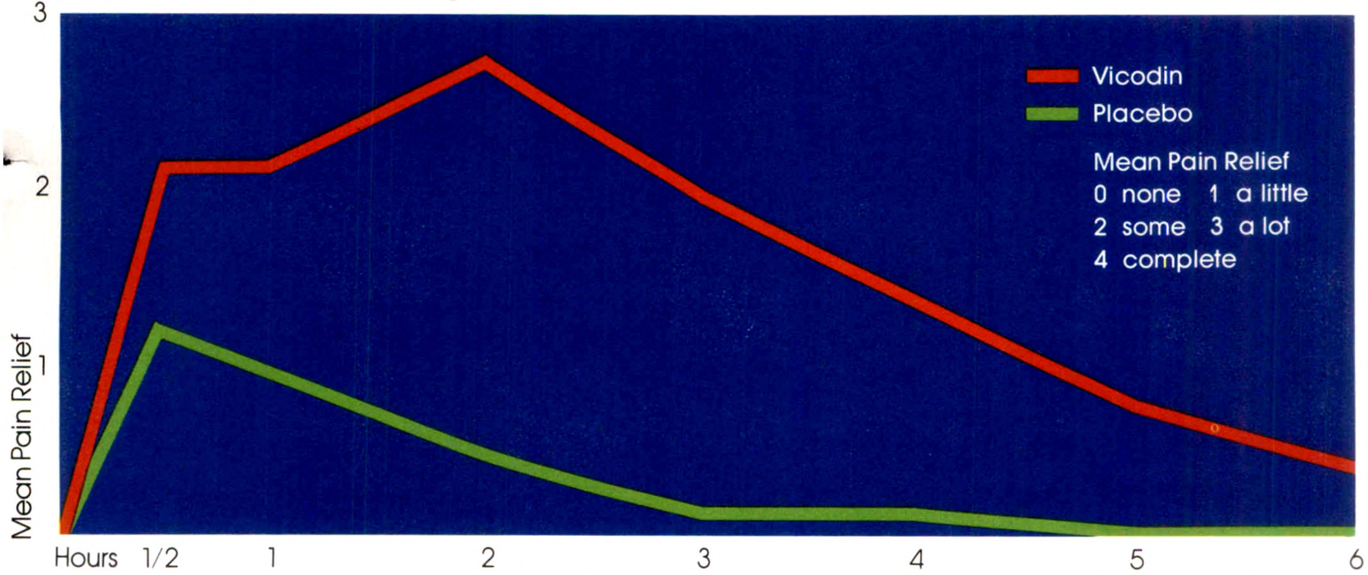
. . .combined with 500 mg. of acetaminophen for improved analgesic activity in moderate to moderately severe pain

Controlled clinical trials in patients with moderate to moderately severe pain have shown that 10 mg. of hydrocodone is approximately equivalent to 60 mg. of codeine in producing total pain relief.[1,2] In addition, 500 mg. of acetaminophen is a clearly more effective dose than the 300 mg. provided by many codeine/acetaminophen combinations.[3,4,5]

1. Data on file at Knoll Pharmaceutical Company (To be published)
2. Hopkinson, J., III: Data on file, Knoll Pharmaceutical Company (To be published)
3. Koch-Weser, J.: New England J. Med. 205:1297, 1976
4. Hopkinson, J. H., et al.: Current Therap. Res. 19:622 (June) 1976
5. Hopkinson, J. H., et al.: Current Therap. Res. 16:194 (March) 1974

A major alternative to combinations of codeine with non-narcotic analgesics

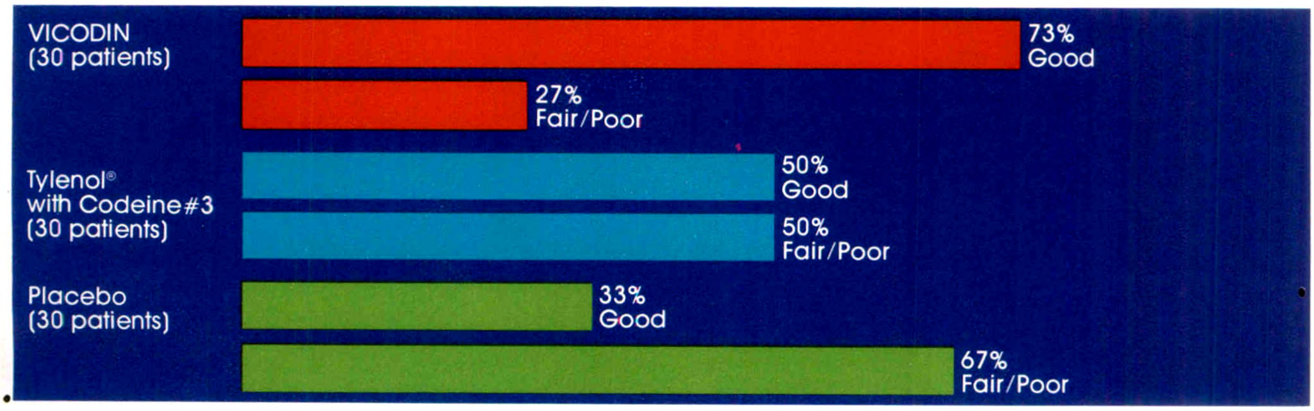
Analgesic effectiveness of VICODIN™ in post operative pain[6]



- In a placebo-controlled double-blind study[6] in patients experiencing moderate or moderately severe pain after surgery, VICODIN was administered to 8 patients and a placebo to 8 others.
- Over a 6-hour evaluation period, VICODIN showed statistically significant superiority in terms of mean pain relief over placebo at hours 2, 3, 4 and 5, after administration.
- In addition, VICODIN was statistically superior to placebo both in terms of total acceptability and total pain relief.

[6] Data on file at Knoll Pharmaceutical Company (To be published)

Analgesic response to VICODIN,™ Tylenol® with Codeine #3, and Placebo in 90 post partum patients[7]



- Three groups of 30 women each with moderate or moderately-severe post partum pain following episiotomy were treated with VICODIN, Tylenol® with Codeine #3, and a placebo.[7]
- In this controlled double-blind study, VICODIN showed statistically significant superiority over Tylenol® with Codeine #3 in terms of overall patient acceptability.

[7] Hopkinson, J., III: Study II, in press.

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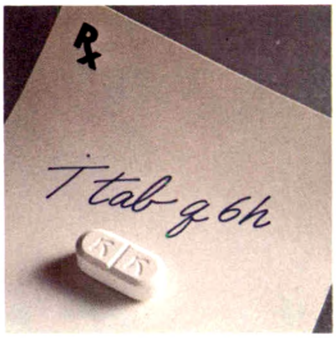
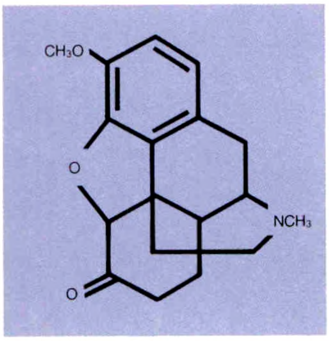
And, prescribing by phone is permissible in most states.



Long-lasting analgesic effects

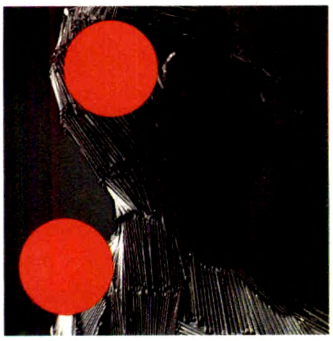
The usual adult dose is one tablet every six hours, as needed.

Dosage is adjusted according to the severity of pain and the response of the patient.



Effective analgesic activity within 30 minutes

Studies[6,7] show that effective analgesic results can be achieved with VICODIN within 30 minutes.



Central and peripheral sites of action for greater pain relief

Hydrocodone in VICODIN™ alleviates pain through central effects while the acetaminophen in VICODIN works at the site of pain as well as on the CNS.

Thus, complementary analgesic effects are achieved with two drugs that work at two different sites.

Description: Each tablet of VICODIN contains:
Hydrocodone Bitartrate 5 mg.
(Warning: May be habit forming.)
Acetaminophen (APAP) 500 mg.

Acetaminophen occurs as a white, odorless crystalline powder, possessing a slightly bitter taste.

The hydrocodone component is dihydrocodeinone, a white, odorless crystalline powder which is derived from the opium alkaloid, thebaine.

Actions: The principal analgesic ingredient, hydrocodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; most of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the hydrocodone in this drug are analgesia and sedation.

Hydrocodone is similar to codeine and methadone in that it retains at least one half of its analgesic activity when administered orally.

This drug also contains the non-narcotic antipyretic-analgesic acetaminophen.

Indications: For the relief of moderate to moderately severe pain.

Contraindications: Hypersensitivity to hydrocodone or acetaminophen.

Warnings: Drug Dependence: Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, VICODIN (hydrocodone bitartrate with acetaminophen) is subject to the Federal Controlled Substances Act.

Usage in Ambulatory Patients: Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, VICODIN should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweight the possible hazards.

Usage in Children: VICODIN should not be administered to children.

Precautions: Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of VICODIN or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: VICODIN should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.

Adverse Reactions: The most frequently observed adverse reactions include light headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: The usual adult dose is one tablet every six hours as needed for pain. Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended above in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. VICODIN is given orally.

Drug Interactions: The CNS depressant effects of this drug may be additive with that of other CNS depressants. See **Warnings.**

Management of Overdosage: Signs and Symptoms: Serious overdose with VICODIN (hydrocodone bitartrate with acetaminophen) is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, criculatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of this drug may, in addition, result in acute hepatic toxicity.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Acetaminophen in massive overdosage may cause hepatotoxicity in some patients. Clinical and laboratory evidence of hepatotoxicity may be delayed for up to one week. Close clinical monitoring and serial hepatic enzyme determinations are therefore recommended.

Treatment of acute acetaminophen overdosage is purely symptomatic.

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PRINTED IN U.S.A. AUGUST 1978

The Relationship between Transfusion and Hypoxemia in Combat Casualties

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The relationship between transfusion and subsequent hypoxemia was examined retrospectively in the records of combat casualties studied by the first three U.S. Army Surgical Research Teams in Vietnam. There was no evident relationship in 425 casualties studied before anesthesia and operation. In 199 casualties studied preoperatively and on at least two of the first three postoperative days, there was no evident relationship in those with injuries not involving the chest or abdomen. Eighteen such casualties received over ten units of blood each (average 24.5) and exhibited subsequent changes in arterial oxygen tension (Pa_{O_2}) which were indistinguishable from those transfused lesser amounts or not at all. Similar observations were made in casualties with injuries to the abdomen, although there was a tendency to lower Pa_{O_2} two days after injury in those heavily transfused. In those with thoracic injury, there were statistically significantly lower Pa_{O_2} on the first two postoperative days in those heavily transfused. Two possible interpretations are considered, one that blood transfusion contributed to hypoxemia, and alternatively, that a greater magnitude of the injuries accounted for both the worsened hypoxemia and the need for more transfusions. The latter was thought more likely. The differences in Pa_{O_2} related to the type of injury exceeded the differences associated with transfusion.

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THERE ARE CONFLICTING STUDIES on the relationship between extensive transfusion and hypoxemia. Collins et al. found no such relationship in 69 combat casualties with peripheral injuries studied preoperatively.[6] The U.S. Naval Surgical Research Teams also found no such relationship but did not present the relevant data in detail.[3] Proctor et al. studied U.S. Marine combat casualties who developed posttraumatic respiratory failure, but did not list transfusion among the possible causes.[15]

Favoring such a relationship were the findings by Moseley and Doty of particulate debris in the lungs of two heavily transfused casualties who died,[14] although Martin et al. in a larger survey of the pathological findings in the lungs of combat casualties did not mention such a relationship.[12] Simmons et al. studied 225 combat casualties and found a significant correlation between transfusion and hypoxemia on the second postoperative day.[19] McNamara et al. reported a significant correlation between the transfusion of over ten units of blood and hypoxemia on the first two postoperative days in combat casualties.[11]

There have been fewer studies in noncombat situations, and these have focussed on the study of microembolization. Reull et al. in a prospective, controlled study reported hypoxemia following transfusion which was less severe in patients transfused through fine filters.[16] During the early, controlled phase of the study, however, it appears that more of the patients receiving nonfiltered blood had injuries to the chest and abdomen. Virgilio et al. recently reported a prospective controlled study in patients undergoing elective operations on the abdominal aorta.[21] There was little evidence of a relationship between transfusion and postoperative hypoxemia, and no differences between the patients who received blood through fine filters versus those who received blood through standard filters.

There are several mechanisms whereby transfusion might cause hypoxemia, of which microembolization is the most recently publicized but perhaps not even the most likely. Because of the markedly conflicting results in published series, we analyzed the data on transfusion and arterial oxygen tension in the combat casualties studied by the first three U.S. Army Surgical

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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Research Teams in Vietnam. The results are subject to several interpretations, but in general do not support a strong cause and effect relationship between extensive transfusion and hypoxemia.

Materials and Methods

The U.S. Army Surgical Research Teams which performed these studies were located in South Vietnam in 1966 and 1967 at the 93rd Evacuation and 3rd Surgical Hospitals in Long Binh, Bien Hoa, and the Mekong Delta, in that sequence. The patients were active duty U.S. Army combat troops except for a few U.S. male civilian construction workers, Vietnamese civilians, and Vietnamese and Korean combat troops. Age was not recorded for all, but the great majority were between 18–22 years old. The interval from wounding to study and treatment was not always known, but for probably at least 90% this was 1½ hours or less. Blood was whole blood (less than 5% red cell concentrates) collected in ACD, NIH solution A, and stored in plastic bags (Fenwal). Only standard gross filters (170 micron pores) were used. Almost all the blood had been collected from active duty U.S. military personnel and their families in the U.S. and Japan. Occasionally, fresh blood was collected at the hospital from local personnel for special circumstances (especially clinical coagulation defects), but this was not common. Data were not collected for all the blood used, but in various samples of blood used at these hospitals during this time, over 80% was beyond 12 days of storage. The blood had been transported into South Vietnam by air and was usually rotated through several distribution points before use. Despite this there seemed to be little evidence of problems due to loss of refrigeration, as great care was taken to ensure proper temperature during transportation.

Arterial blood samples were obtained in heparinized plastic syringes by percutaneous arterial puncture, immediately placed in ice, and quickly analyzed in duplicate in a special research laboratory on a Model 113 blood gas analyzer (Instrumentation Laboratories), using gases of known composition for equilibration. Records of transfusion and pertinent events were kept by the teams themselves on standard anesthesia records or on special data sheets. The teams were regularly called when casualties arrived (almost always by helicopter). Not all casualties were studied; at various times there was special interest in casualties with penetrating wounds of the thorax, blast injuries, head injuries, traumatic amputations, fractured femurs, and others, but at all times the most severely injured were studied regardless of special interests. Thus, most of the heavily transfused but only a small percentage of the nontransfused were included.

TABLE 1. *Arterial Oxygen Tensions, Mean ± SD, (n), of Casualties Studied Before General Anesthesia, According to Type of Injury and Amount of Blood Transfused*

	Peripheral Injuries	Trunkal Injuries
Not transfused	89.93 (213) ± 14.74	76.94 (155) ± 17.47
All transfused	88 (30) ± 12.98	74.37 (27) ± 15.94
Transfused 1–5 units	88.91 (22) ± 9.88	72.91 (23) ± 16.19
Transfused >5 units	85.5 (8) ± 19.87	82.75 (4) ± 13.1

In the present study, all those with head injuries, burns, or obvious aspiration were excluded. Casualties were classified as having peripheral injuries if there was no evidence of direct injury in the abdominal or thoracic cavities, abdominal injuries if there was damage to abdominal contents even if peripheral injuries were also present, and thoracic injuries if there was direct injury in the thoracic cage even if both other types of injury were present.

The first part of the study deals with pre- and post-transfusion data before the administration of general anesthesia. This includes casualties never transfused. The second part of the study deals with casualties studied before and after operation. These data include only those casualties for whom there were studies before general anesthesia and on at least two of the first three postoperative days, who are considered in the greatest detail. Data are also given on a larger number of casualties who were studied before and on the first day after anesthesia.

Data on some of these casualties have been reported elsewhere.[6,19] Over half the casualties studied here are reported for the first time, and data on those reported previously are presented in greater detail and are analyzed differently.

Results

The data for 425 casualties studied before the administration of general anesthesia are given in Table 1. These are all different casualties, that is, the same casualty was not studied before and after transfusion. There is no evidence of an immediate suppressive effect of transfusion on arterial oxygen tension (Pa_{O_2}). The differences in mean Pa_{O_2} between those with peripheral injuries and those with trunkal injuries were statistically significant (p .001) for those not transfused, and for those transfused one to five units of blood.

A smaller number of casualties (199) were studied before and on at least two of the first three days following injury. These data are given in Table 2 by type of injury and by ranges of the volume of blood transfused. In those with peripheral injuries only, there was no discernible association between transfusion and the subsequent development of hypoxemia. The heavily transfused group is noteworthy: 18 patients who received an average of 25 units of blood on the day of injury (minimum 12 units) showed no perceptible difference in Pao$_2$ through the first three postoperative days from those transfused lesser amounts or not transfused at all. In all except the group receiving one to five units of blood, the average of the lowest Pao$_2$ recorded during the first three postoperative days was statistically significantly different from the preoperative values for the same patients.

In those with abdominal injuries, there was also not a statistically significant difference between those transfused and those not transfused, although the most heavily transfused group had somewhat lower mean Pao$_2$ on the second and third postoperative days than did most other groups with abdominal injury. The means of the lowest recorded Pao$_2$ in the postoperative period were statistically significantly different for the corresponding preoperative values for all transfused groups, but not for those not transfused. In addition, the mean Pao$_2$ for Day 2 and Day 3 were statistically significantly different from the preoperative values for those receiving over ten units of blood, and for Day 3 for those receiving one to five, but not six to ten units of blood. When compared to the corresponding values for casualties with peripheral injuries, the patients with abdominal injuries tended to be more hypoxemic, but this was statistically significant only for the lowest recorded values in those receiving one to five units of blood.

The patients with thoracic injury were different. They were significantly more hypoxemic than both other groups, especially those with peripheral injuries.

TABLE 2. *Amount of Blood Transfused (Mean ± SD) and Arterial Oxygen Tensions (Pao$_2$, Mean ± SD) of Casualties Studied Before and on at Least Two of the First Three Postoperative Days*

Transfusion Range (Units)	No. Units	Pre	Day 1	Day 2	Day 3	Lowest*
			Peripheral Injuries			
Not transfused	—	83 (18) ± 10.98	77 (18) ± 15.24	79.5 (18) ± 13.74	77.67 (6) ± 11.81	73.39 (18) ± 14.05
1–5	3.18 (24) ± 1.37	86.75 (24) ± 15.07	84.79 (24) ± 12.89	84 (21) ± 10.33	81.55 (11) ± 12.35	79.12 (24) ± 11.69
6–10	7.92 (12) ± 1.44	88.42 (12) ± 13.97	77.42 (12) ± 11.07	79.75 (12) ± 14.05	76 (7) ± 6.27	73.42 (12) ± 11.41
>10	24.53 (18) ± 11.94	87.11 (18) ± 18.47	75.38 (16) ± 15.79	76.94 (17) ± 16.93	79.54 (13) ± 11.25	69.94 (18) ± 16.38
			Abdominal Injuries			
Not transfused	—	80.67 (9) ± 15.43	78.5 (8) ± 18.19	78.33 (9) ± 13.32	75.25 (4) ± 18.26	71.56 (9) ± 15.87
1–5	3.23 (16) ± 1.15	86.38 (16) ± 14.45	78.06 (16) ± 15.08	77.5 (14) ± 9.94	71.83 (12) ± 11.29	68.94 (16) ± 9.29
6–10	7.75 (10) ± 1.82	85.4 (10) ± 12.74	76.2 (10) ± 16.57	80.71 (7) ± 11.4	82 (9) ± 12.66	70.1 (10) ± 12.08
>10	25.18 (10) ± 9.59	87.3 (10) ± 8.38	76.1 (10) ± 20.22	71.6 (10) ± 19.6	71.89 (9) ± 20.66	65.2 (10) ± 19.66
			Thoracic Injuries			
Not transfused	—	71.52 (24) ± 20.63	72.38 (24) ± 14.22	77.27 (15) ± 14.13	72.75 (16) ± 16.1	66.79 (24) ± 12.56
1–5	2.97 (31) ± 1.45	70.42 (31) ± 14.5	70.77 (26) ± 16.65	69.59 (27) ± 15.12	70.81 (26) ± 15.79	64.42 (31) ± 16.35
6–10	7.93 (14) ± 1.49	70.86 (14) ± 22.02	63.36 (14) ± 12.8	64.36 (14) ± 10.2	68.62 (13) ± 12.92	59.73 (14) ± 10.51
>10	21.36 (13) ± 8.11	72.31 (13) ± 16.01	58.58 (12) ± 14	59.25 (12) ± 16.93	64.75 (12) ± 17.35	55.15 (13) ± 13.61

* "Lowest" means lowest Pao$_2$ value in the first three postoperative days.

TABLE 3. *Summary of Statistical Differences Between Mean Pa_{O_2} of Patients with Thoracic Injuries and Corresponding Groups of Patients with Peripheral and Abdominal Injuries. Based on t-test for Unpaired Data*

Transfusion (Units)	Pre	Day 1	Day 2	Day 3	Lowest
			Peripheral vs. Thoracic		
None	.05				
1–5	.001	.01	.001		.001
6–10	.05	.01	.01		.01
>10	.05	.01	.01	.02	.02
			Abdominal vs. Thoracic		
None					
1–5	.001				
6–10		.05	.01	.05	.05
>10	.02	.05			

Values are probability (p) of there being no true statistical difference; only p .05 or less are given.

The statistical differences are summarized in Table 3. There were also differences between those transfused heavily and those not transfused. These are summarized in Table 4. Clearly the heavily transfused patients with thoracic injuries were more severely hypoxemic on the first two postoperative days than were nontransfused casualties with thoracic injuries.

The data on all casualties studied preoperatively and on the first postoperative day are presented in Table 5. It is a larger group (284) than those studied for the longer period, and it includes most of those same patients. The results are not very different. The degree of statistical differences, summarized in Table 6, are somewhat greater because of the larger numbers, but the pattern of differences is the same.

Discussion

There are many potential causes of hypoxemia in injured patients, but there are a number of mechanisms by which transfusion specifically might cause hypoxemia (Table 7).[4] Of these, perhaps the most significant is circulatory overloading. This is most likely to occur when very large volumes of fluid are shed and infused and small therapeutic errors become magnified, or when the function of the heart is impaired or vulnerable. The heavily transfused casualties in this series received very large volumes of blood plus supplemental salt solutions. Monitoring was by clinical signs and by central venous pressure; there was no monitoring of pulmonary capillary wedge pressures. Despite this, there seemed to be little evidence of serious therapeutic overinfusion. A relatively conservative approach to the use of supplemental salt solutions may have aided in this, but there is no clear evidence on this point. The function of the heart in these patients was probably about as excellent as can be expected in any series of similarly injured patients. A random civilian population containing individuals with an impaired or vulnerable cardiac functional capacity might have shown less tolerance to the marked shifts in blood volume that must have occurred before and during resuscitation. Even such changes when they occur, however, are not a result of the transfused blood itself.

TABLE 4. *Statistical Differences in Mean Pa_{O_2}'s Between Groups of Patients with Thoracic Injuries, Based on t-test for Unpaired Data*

	Day 1			
	Not Transfused	Transfused 1–5 Units	Day 2 Not Transfused	Lowest Not Transfused
Transfused 6–10 units			.01	
Transfused over 10 units	.01	.05	.01	.02

Values are probability (p) of there being no true statistical difference; only p .05 or less are given.

Immunologic reactions can cause pulmonary edema, even during single unit transfusions without circulatory overloading.[22] Such reactions probably involve certain proteins in the plasma of the transfused blood. Hemolytic transfusion reactions are a classical cause of disseminated intravascular coagulation, which many believe can itself cause significant respiratory insufficiency.[4] During rapid transfusion of multiple units of blood, immunologic reactions between units of transfused blood may occur with the recipient as victim, not necessarily as participant.[7]

There is provocative older evidence indicating that certain plasma proteins become denatured or altered during storage, and that certain fractions of stored plasma can in fact be lethal in certain experimental models.[18] Contact of whole blood with glass may have had a similar effect in hemorrhaged dogs.[8,17] Similar mechanisms are thought to be important in prolonged cardiopulmonary bypass in which the blood is exposed to foreign surfaces.[10] Recently, elevated levels of prekallikrein activator (from Factor XII) were implicated in hypotensive reactions in patients receiving plasma products processed in a certain way.[1] Whether these are native proteins that are truly denatured or whether they are activated inflammatory mediators, many of these materials cause increases in capillary permeability. It is not known whether changes of this type occur during liquid storage of citrated blood in plastic bags at 4°, but it seems possible.

Berman et al. have implicated the plasticizer diethyl-

TABLE 5. *Arterial Oxygen Tensions (PaO_2, Mean ± SD) of Casualties Studied Before Anesthesia and on the First Postoperative Day, According to Type of Injury and Amount of Blood Transfused*

Transfusion (Number of Units)	Peripheral			Abdominal			Thoracic		
	n	Pre	Day 1	n	Pre	Day 1	n	Pre	Day 1
None	46	85.46 ± 11.81	82.74 ± 11.8	13	83.85 ± 17.8	78.73 ± 15.29	35	71.34 ± 17.26	72.43 ± 12.89
1–5	49	89.61 ± 14.45	84.88 ± 12.67	21	84.67 ± 13.38	79.14 ± 13.88	32	73.16 ± 16.01	71.09 ± 17.46
6–10	18	87.83 ± 14.45	79.94 ± 10.58	12	83.5 ± 12.61	75.77 ± 15.47	15	70 ± 21.48	62.8 ± 12.52
>10	19	86.21 ± 17.88	78.84 ± 14.88	11	84.55 ± 12.11	76.1 ± 20.22	13	72 ± 15.52	59.08 ± 13.52

hexylphthalate in an increase in pulmonary capillary permeability in transfused and infused rats.[2] This material accumulates at a constant rate in blood stored in plastic bags. We found no evidence of change in oxygenation in swine massively transfused with blood stored in plastic, but the animals were not followed more than several hours after transfusion.[13]

Microembolization has received the most attention recently as a possible cause of pulmonary insufficiency after extensive transfusion. Microaggregates accumulate more or less steadily during storage and are too small to be removed by standard filters. Studies in dogs suggest that such a lesion occurs, but studies in primates have not borne this out.[20] A prospective clinical study by Reull et al. suggested that hypoxemia occurs after extensive transfusion and can be prevented by the use of fine filters during transfusion.[16] The groups of patients in the controlled part of the study seemed not to be comparable in the types of injuries, however. A recent prospective study by Virgilio et al. on patients undergoing elective operations on the abdominal aorta found little evidence of transfusion-induced hypoxemia and no beneficial effects from the use of fine filters.[21]

Finally, stored blood is cold, acidotic, and hyperkalemic. If it is infused rapidly through central catheters, the pulmonary capillary bed may receive blood with some of these characteristics. Presumably this could be damaging, but direct evidence is slight.

There are a number of imperfections in the present study. The present data are retrospective; many of these patients were studied because of interest in other conditions. These data do not represent the results of comprehensive study of all injured patients who arrived for treatment during a specified period of time. There do not seem to be any systematic biases in the choice of patients that would alter these results, however. The most seriously injured patients were always studied; it was the less injured who were chosen for study from among larger numbers available. Similarly, the sampling after operation was often incomplete. Some of this was because of death or early transfer of casualties out of the country, but some was because a specific protocol calling for such sampling was not in effect at the time. Again, the most seriously injured were almost always studied well into the period of recovery, and it was among the less seriously injured that sampling was discontinued sooner than three days postoperatively. It is not apparent that this biased the results in the less seriously injured; the data for the heavily transfused are rather solid.

These casualties were previously healthy young

TABLE 6. *Statistical Differences in Mean PaO_2's Between Patients with Thoracic Injuries and Corresponding Patients with Peripheral or Abdominal Injuries Studied Before and on the First Day Following Injury, Based on t-test for Unpaired Data*

Transfusion (Number of Units)	Peripheral vs. Thoracic		Abdominal vs. Thoracic	
	Pre	Day 1	Pre	Day 1
None	.001	.001	.05	
1–5	.001	.001	.01	
6–10	.01	.001		.05
>10	.05	.001	.02	.05

Values are probability (p) of there being no true statistical difference; only p .05 or less are given.

TABLE 7. *Some of the Possible Mechanisms by Which Extensive Transfusion Might Cause Hypoxemia*

Circulatory overloading
Immunologic reactions
Hemolysis-disseminated intravascular coagulation
Activated inflammatory mediators
Denatured plasma proteins
Plasticizers
Microemboli
Cellular aggregates
Cold, acidosis, hyperkalemia

adult males, medically screened and athletically conditioned before injury. Their cardiorespiratory systems were probably near the maximum possible functional status for the injuries sustained. Most were treated soon after injury. These conditions will not apply to the population-at-large of heavily transfused patients. Such patients as we studied would be expected to better withstand additional injury to the lungs. On the other hand, the blood that was used was distinctly older than the average age of blood transfused in the United States, especially to extensively bleeding patients. If the presumed lesion in the stored blood increases with duration of storage, then these casualties were exposed to particularly severe challenges. Only standard (170 micron pore) filters were used, and these were often used for multiple units of blood under the press of rapidly transfusing multiple casualties simultaneously, so that even some gross clots were observed in the transfusion lines. Civilian casualties rarely sustain the massively destructive wounds characteristic of warfare. Blast and high kinetic energy missile wounds are infrequent in civilian practice but were common in the heavily transfused combat casualties.

Finally, arterial oxygen tensions were the criteria for pulmonary impairment in the present study. Various other changes might have occurred in these patients; increased interstitial edema might have been detected by studying compliance, which was impractical in these circumstances. Clearly, some degree of retention of fluid in the lungs can occur without impairing oxygenation.[5,9] Nevertheless, oxygenation is the critical function in patients with posttraumatic pulmonary insufficiency and would be expected to be impaired with most clinically significant degrees of damage to the lungs by the possible mechanisms linking transfusion with pulmonary damage.

The present study contains evidence both for and against a relationship between transfusion and hypoxemia. The results in the patients with peripheral injuries were rather dramatically negative. A significant number of casualties received over two blood volumes in transfusion with no detectable effect on Pa_{O_2} during the three days following transfusion. This observation alone must cast doubt on a major effect of transfusion on the exchange of gas in the recipient's lungs, and clearly indicates that at least some patients can be heavily transfused with whole blood without special equipment or precautions and with little or no effect on oxygenation.

On the other hand, casualties with abdominal injuries showed suggestive decreases in Pa_{O_2} associated with transfusion, and those with thoracic injuries showed a strong correlation in the postoperative period. In both groups the changes were greatest in those receiving the most blood. The patients with thoracic injuries were more hypoxemic than those with peripheral injuries before operation and throughout the postoperative period, whether transfused or not. Those with abdominal injuries had suggestively, but not significantly lower Pa_{O_2}. This raises the possibility that there was indeed a detrimental effect of transfusion on pulmonary function, but that it was subliminal by itself and/or strongly additive with other factors that produced hypoxemia. It was thus manifested in those whose injuries predisposed them to hypoxemia postoperatively. Such a mechanism would have to have had a moderately delayed effect, as it was not evident preoperatively. This would eliminate the usual kinds of microembolization from consideration but would be compatible with the several potential mechanisms which might increase pulmonary capillary permeability. There is no direct evidence to refute such an interpretation of these data.

We believe, however, that the more likely explanation relates to the injuries themselves. By direct observation it was obvious that in general the magnitude of the injuries paralleled the requirements for transfusion and the magnitude and duration of the operations. Unfortunately, we don't have sufficient data to objectively corraborate the latter assumptions, but common sense and the experience of those who performed these studies indicate they are legitimate. When the injuries were such as to produce hypoxemia in themselves, especially injuries to the lungs, the resulting hypoxemia would understandably be greater. The weakness of this interpretation is that the heavily transfused patients were not more hypoxemic on admission. There is no ready explanation for this except that hypoxemia from pulmonary contusion seemed to become greatest one to two days after injury, and these casualties were usually studied and treated very soon after injury. Considering the entire pattern of findings, this interpretation seems clearly preferable to that invoking a direct causal relationship between transfusion and hypoxemia.

Finally, it must be emphasized that the differences in oxygenation related to the type of injury were greater than those possibly related to transfusion, even where such were noted. It is mandatory to carefully consider the types of injury in evaluating changes in pulmonary function in injured patients. This seems obvious, but is sometimes ignored.

Acknowledgments

The authors are indebted to the professional staffs of the 93rd Evacuation and 3rd Surgical Hospitals, who gave their complete cooperation and support to the various research teams, and to the technical staffs who were an essential part of the research teams in Vietnam.

These studies were carried out while the authors were members of the Walter Reed Army Institute of Research; the conclusions and statements contained herein are those of the authors and do not necessarily reflect those of the U.S. Army Medical Corps or the Surgeon General.

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DISCUSSION

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): I would like to express our appreciation to Dr. Collins for doing something about removing the confusion that has existed in this matter of transfusion versus injury as a cause for pulmonary dysfunction.

The important thing in the studies, as Dr. Proctor presented some time ago, is that, as time progresses, the major injury patients tend to develop is infection, and our own experience has shown that infection is the common denominator causing the shunt phenomenon. We presented a series of cases which have since been enlarged, in which we had people with automobile accidents or gunshot wounds to the liver, all requiring lobectomies, all having not less than 12 units of blood transfusion involved in the treatment; in those who recovered—who survived the operation but did not become infected—there were no pulmonary problems, essentially, and in those who subsequently became infected, on the fourth, fifth, sixth day, there was a progressive deterioration of the pulmonary function.

One of those cases with an aortic injury was transfused with 80 units of blood. He didn't have a single thing wrong with his pulmonary function, and he was on a respirator, until such time as he became infected, and within 24 hours his function had deteriorated remarkably.

I would like to ask Dr. Collins one question which is purely technical. I think the presentation would be stronger if we knew what the shunt calculation, or an estimate of the shunt, might be, because undoubtedly some of these patients had to be on respirators, and one would want to know that the FiO_2 or something comparable, was being looked at, when you presented the figures on arterial oxygen tension.

DR. F. WILLIAM BLAISDELL (San Francisco, California): We very much enjoyed Dr. Collins' presentation. I would just like to add one other comment.

The lung is capable of handling a large amount of foreign material without any significant effect on pulmonary function. These studies of massive transfusion further document this fact since the amount of sludge administered along with 10 units of old blood is considerable.

I believe that the lung's tolerance to transfusion emboli is related to its reserve, so I would speculate that the patients who had thoracic injury had less pulmonary reserve. Thus, in this patient, a given amount of sludge would be reflected in a greater alteration in pulmonary function than it would in a patient with normal lung function. In addition, I believe that a good bit of the lung damage relates to intravascular clotting, the degree of which correlates well with the extent of soft tissue damage a given patient has. Someone with good lungs, peripheral injuries and requiring a moderate amount of transfusion, for instance, would be expected to have little lung function alteration, but given a patient with damaged lungs, more soft tissue injury, and the same amount of transfusion, you might see quite a bit of alteration in pulmonary function.

One of the reasons we are no longer seeing respiratory failure in the first few days following injury is because we now monitor pulmonary function closely and introduce positive pressure ventilation early in relation to the type of injury presented in Dr. Collins' series. As a result, by keeping the lung expanded, it is possible to prevent the acute phase of respiratory distress; we only see the patient develop respiratory distress at a later date whenever infection supravenes.

Dr. James V. Maloney (Los Angeles, California): I offer a hypothesis which supports Dr. Collins's speculation that the hypoxia in these battle casualties, although associated with the amount of blood administered (and, therefore, with the degree of trauma), is not causally related. I refer to the proceedings of a conference held by the National Research Council, published in the *Journal of Trauma*, in 1968. The conference was called to evaluate a new syndrome called the wet lung which was occurring in Viet Nam casualties.

Occasional casualties were hypoxic and required the use of respirators. When the data were presented, it was noted that most of the injured received between five and 15 l of Ringer's lactate solution rather than colloid replacement, which had been characteristic of the therapy used in the Korean War.

The therapy was based on the assumption that it was safe to give huge volumes of crystalloid so long as central venous pressure did not rise. It was apparent that the physicians and surgeons caring for these casualties were not aware of the fact that crystalloid, given in large amounts, may produce pulmonary edema and hypoxia without raising central venous pressure (because of the short transit time of crystalloid in the vascular space and because left atrial pressure, not central venous pressure, is the critical measurement).

Following that conference, Ringer's lactate was used more judiciously in Viet Nam. In a subsequent conversation with a surgeon who is here today, Dr. Thomas J. Whelan (then Deputy Surgeon General) I learned that when the therapeutic method was changed in Viet Nam, using more colloid and less crystalloid, the problem of wet lung virtually disappeared.

The amount of crystalloid given to those patients was related to the degree of trauma, as was the amount of blood. Since crystalloid overload may be associated with hypoxia, we have a reasonable explanation for the association of hypoxia, the degree of trauma, and the amount of blood transfused. This hypothesis supports Dr. Collins's data, showing a noncausal relationship between blood transfusion and the hypoxia of "Viet Nam lung."

Dr. John A. Collins (Closing discussion): Dr. Clowes was one of the first, and the most persistent, to point out the relationship between infection and pulmonary dysfunction, and he's entirely right. This is one of the reasons why we focused on the first three days after injury. If we extended the studies further, it turned out that the heavily transfused patients had a higher incidence of serious infection. That's when they got into trouble, ended up on ventilators and developed huge shunts.

There again we face the question of whether the transfusion had something to do with the infection, or whether it was, again, coincidental but not causally related. It's a very difficult clinical problem, to try and pick apart the effects of transfusion, because some of these casualties had to have oxygen-delivering capacity restored. It's really impossible to perform the perfect study, have the same injury with treatment with and without blood. Until we get something that delivers oxygen that's not blood, we're not going to have answers to some of these questions.

The data that we presented, Dr. Clowes, were all based on spontaneous breathing of room air. We did not include patients who were on respirators postoperatively. It turns out, surprisingly, that this was very few patients in the groups that we looked at. In fact, there were none in the groups that would otherwise have fallen into the studies of peripheral injury. There were only one or two in the group with abdominal injury. Most of them ended up in the group with thoracic injury. So, if anything, it would have made the differences more marked in the direction that we already showed, because we would have had larger shunts and lower PO_2's in those with thoracic injury and the same kind of a result in those with peripheral injury.

Dr. Blaisdell has opted for the first of my two proposed interpretations of the data, which I think is perfectly legitimate. There's nothing in the study that we did that proves one over the other. I gave you my interpretation of it as somebody who was there, observing what was happening at the time, but we pointed out in the discussion that the other interpretation is probably equally valid. Again, I find it a little hard to believe that there would be absolutely no detectable difference in those with peripheral injuries and such a marked difference in those with thoracic injuries if transfusion were causally related.

Dr. Maloney has attempted to get me into the controversy about salt water, but I'll do my best to avoid it. In the areas where we were working salt water was used very judiciously and very conservatively. There was at that time another end of the country with another military service, based on salt water, which seemed to have a propensity to bring their patients more into the salt water era. It was our impression that they had more trouble with the lungs than we had, but I'm certainly not going to say that it was causally related to salt water.

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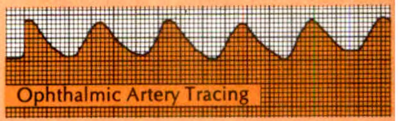

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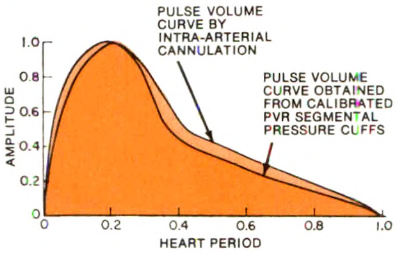

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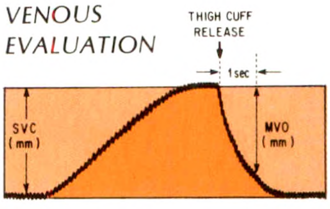

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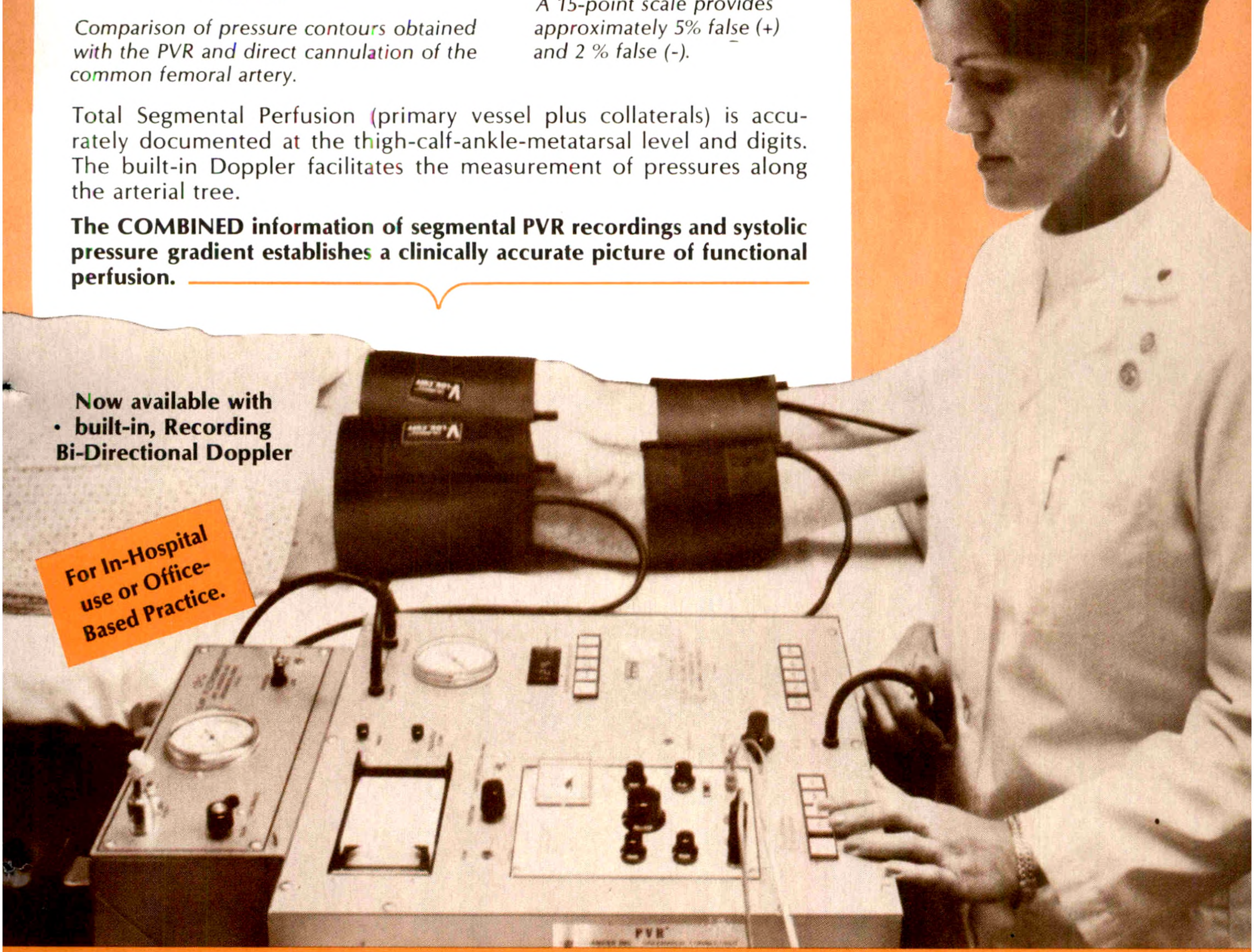

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Biliary tract infections due to *Escherichia coli*, various strains of streptococci, *Proteus mirabilis, Klebsiella* species and *Staphylococcus aureus.*

Bone and joint infections due to *Staphylococcus aureus.*

Genital infections (i.e., prostatitis, epididymitis) due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterococci.

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

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Warnings: BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

Precautions: Prolonged use of 'Ancef' may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

Adverse Reactions: The following reactions have been reported: **Hypersensitivity:** Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred. **Blood:** Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred. **Hepatic and Renal:** Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment. **Gastrointestinal:** Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported. **Other:** Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

How Supplied: Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., or 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 500 mg. or 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

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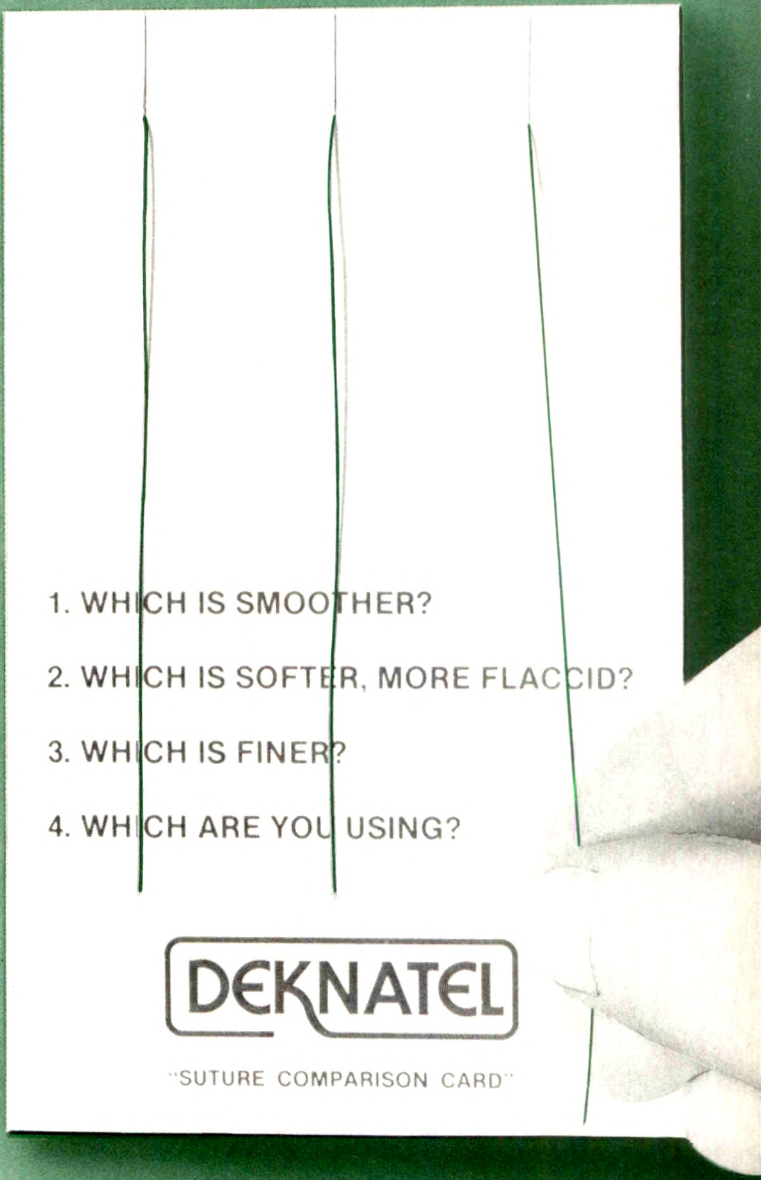

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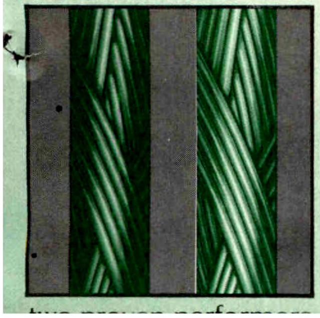

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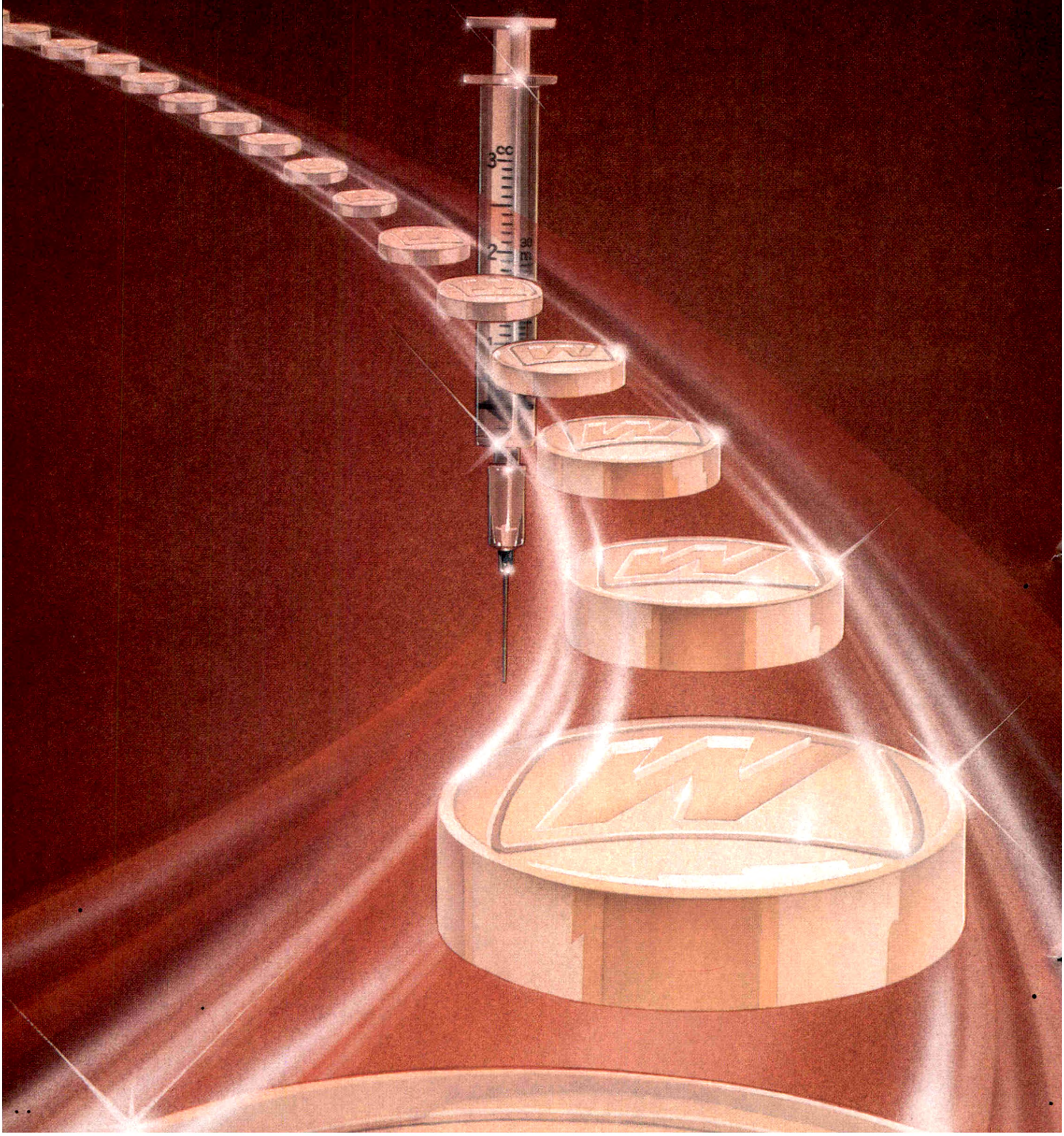


Potent - Dependable - Nonopiate

Talwin® HCl 50 mg.
brand of . equivalent to 50 mg. base
pentazocine HCl tablets, NF

Relieves pain as well as 60 mg. of codeine.

MILD ANALGESICS OFTEN DON'T WORK:

In a double-blind single dose study involving 225 adult inpatients, the comparative efficacy of 650 mg. aspirin, 65 mg. dextropropoxyphene, and 50 mg. pentazocine for relief of postoperative pain was recorded.[1]

- All patients were suffering from moderate or severe pain.
- Pregnant women as well as patients with known renal, respiratory, cardiac, or hepatic insufficiency were excluded.
- The onset of action of pentazocine was rapid.
- Although aspirin, dextropropoxyphene, and pentazocine produced significant relief from pain, pentazocine was significantly more effective at a half hour.
- Side effects were recorded for 16 patients: in the aspirin group 2 patients complained of drowsiness and 1 of dizziness. In the dextropropoxyphene group 5 patients vomited and 3 patients complained of drowsiness or dizziness, while 5 patients who had received pentazocine complained of dizziness.
- Pentazocine should be an oral analgesic of choice for treatment of postoperative pain.

Opiates are too addictive, too restrictive:

"Despite their potent analgesic action, the morphine-like analgesics have disadvantages that limit their usefulness: respiratory depression, nausea, vomiting, constipation, cardiovascular effects (hypotension, bradycardia), histamine release, and in some patients, an increase in intracranial pressure. Other adverse reactions include miosis, spasm of the biliary and urinary tracts, and rarely, hypersensitivity phenomena (urticaria, rash, and anaphylactic reactions). Frequent repeated use produces psychic and physical dependence."[2]

Oral Talwin shows infrequent occurrence of certain adverse effects as:

- Severe respiratory depression
- Hypotension
- Constipation
- Urinary retention
- Tachycardia

Among RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions—hallucinations (usually visual)—have cleared spontaneously within a period of hours. Withdrawal symptoms after prolonged use of Talwin for the relief of pain have rarely been reported, even when administration was abruptly discontinued. There have been a few reports of dependence with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

For Continuing Postsurgical Pain Control

Talwin® HCl 50 mg.
brand of . equivalent to 50 mg. base
pentazocine HCl tablets, NF

1 or 2 tablets every three or four hours

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Nonopiate

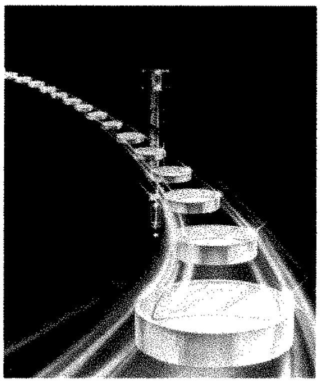
Talwin® HCl 50 mg.

brand of . equivalent to 50 mg. base

pentazocine HCl tablets, NF

Relieves pain of a moderate to severe nature.

Usual initial adult dose is 1 tablet every 3 or 4 hours.



Please consult full prescribing information before prescribing. A summary follows:
Talwin HCl is intended for the relief of moderate to severe pain. One 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. Talwin is a weak narcotic antagonist with sedative activity.

Contraindication

Hypersensitivity to pentazocine.

Warnings

Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin HCl should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions

Oral Talwin has been rarely reported to cause respiratory depression. It should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

Adverse Reactions

Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations; and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently, flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, paresthesia, toxic epidermal necrolysis.

Dosage and Administration

Adults: The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg. Tolerance is rare. Abrupt discontinuance following chronic use has rarely caused withdrawal symptoms.

Overdosage

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

References

1. Kay B: A clinical comparison of orally administered aspirin, dextropropoxyphene and pentazocine in the treatment of postoperative pain. *J Int Med Res* 2:149-152, 1974.
2. AMA Department of Drugs: *AMA Drug Evaluations*, ed 3. Littleton, Mass, Publishing Sciences Group, Inc, 1977, pp 327-328.

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property...of being inactivated by only one aminoglycoside-inactivating enzyme."

Yow MD, An Overview of Pediatric Experience with Amikacin. *Am J Med* (special issue): 167-171, June 1977.

"The standard dose of amikacin usually produces a peak serum concentration which is five times the MIC of most pathogens."

Trenholme GM, McKellar PP, Rivera N, et al: Amikacin in the treatment of gram-negative pneumonia. *Am J Med* 62:949-953, June 1977.

"When these 17 patients, who had previously failed to respond to gentamicin therapy, were treated with amikacin, the response was favorable in 16."

Tally FP, Gorbach SL: Review of 152 patients with bacteremias treated with amikacin. *Am J Med* 62:940-944, June 1977.

"In general, against many gram-negative bacterial species, amikacin is the most effective antibiotic currently available for use..."

Marget W, Reindke B, Versmold H: use of amikacin in a hospital for children: Microbiological and clinical studies. *J Infect Dis* 134 (suppl): S412-S419, November 1976.

"...in combination with high doses of carbenicillin or ticarcillin in patients with renal failure, there is less chance of interaction...when it is amikacin."

Holt HA, Broughall JM, McCarthy M, et al: Interactions between aminoglycoside antibiotics and carbenicillin or ticarcillin. *Infection* 4 (2):107-109, 1976.

"Despite extensive use over a three year period...we have not encountered additional instances of Enterobacteriaceae resistance to amikacin therapy..."

Doughty SC, Martin RR, Greenberg SB: Treatment of hospital-acquired infections with amikacin. *Am J Med* (special issue): 53-57, June 1977.

the empiric agent of choice for patients with serious sepsis."

Hewitt WL, Gram-Negative Sepsis Symposium, Boston, Massachusetts, January 24, 1976.

"All isolates were inhibited by amikacin and 95% were killed by concentrations achievable in serum with recommended doses."

Leonard JM, McGee ZA, Alford RH: Gentamicin-resistant bacillary infection. *Arch Intern Med* 138:201-205, Feb. 1977.

"All serum levels obtained within three hours following a dose of amikacin exceeded the MIC's of the infecting organisms..."

Pollock AA, et al: Amikacin therapy for serious gram-negative infection, JAMA 237:562-564, Feb. 1977.

"High serum levels of amikacin were obtained with no evidence of renal or ototoxicity."

Eller JJ, et al: Amikacin treatment of pseudomonas pneumonia in cystic fibrosis patients with advanced pulmonary involvement. *Am J Med* (special issue): 179-185, June 1977.

"...amikacin is effective therapy for severe gram-negative infections and is no more ototoxic or nephrotoxic than gentamicin."

Smith CR, Baughman KL, Edwards CG, et al: Controlled comparison of amikacin and gentamicin. *N Engl J Med* 296:349-353, Feb. 1977.

"...amikacin provides the physician with a better chance of obtaining therapeutic blood levels above and beyond the MIC of the organism in question."

Klainer AS, Five questions: A comparative analysis of the newest aminoglycoside, film Sept. 1977.

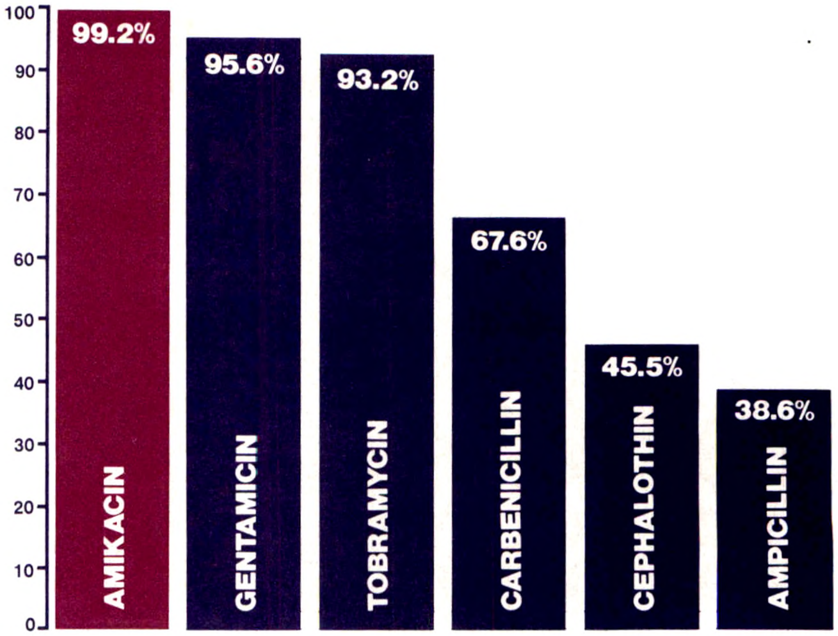
"...only one enzyme found in gram-negative bacteria affected amikacin potency, whereas six enzymes affected gentamicin and sisomicin; five, kanamycin and tobramycin and four, netilmicin."

Price K, et al: Amikacin activity, *Am J Med* (special issue) 14-24 June 1977.

Can any hospital antibiotic be this good?

In-vitro superiority against today's hospital pathogens

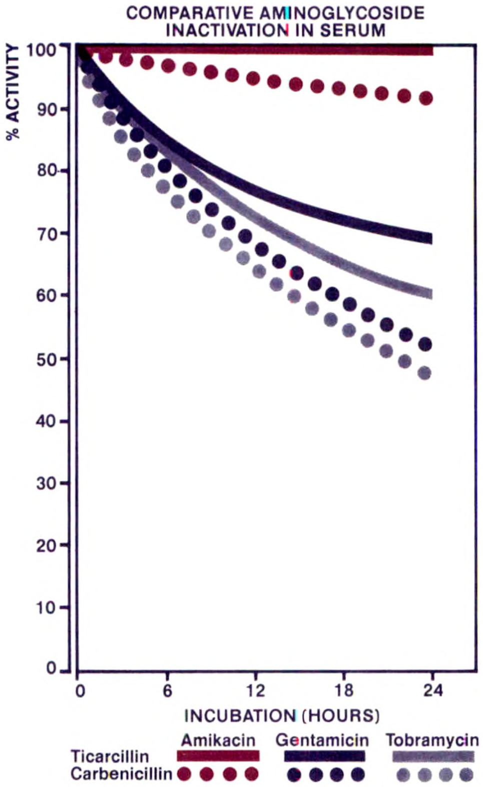
Against 409 bacterial isolates, Amikin® (amikacin sulfate) activity was compared to leading injectable antibiotics. *None* of these agents inhibited as high a percentage of strains as did Amikin.



Susceptibility determined by the agar dilution test method, data on file, Bristol Laboratories. Caution, *in vitro* data cannot be directly correlated to clinical effectiveness.

Least inactivated in combination

When carbenicillin or ticarcillin is combined *in vitro* with ordinary aminoglycosides, a significant reduction in aminoglycoside activity may occur in patients with renal impairment. Virtually uneffected in the presence of ticarcillin, Amikin is also minimally compromised by carbenicillin...while other aminoglycosides may lose up to 50% of their activity!



Adapted from Holt HA, Broughall JM, McCarthy M, et al: Interactions between aminoglycoside antibiotics and carbenicillin or ticarcillin, *Infection* 4(2):107-109, 1976.
Caution, *in vitro* data cannot be directly correlated to clinical effectiveness.

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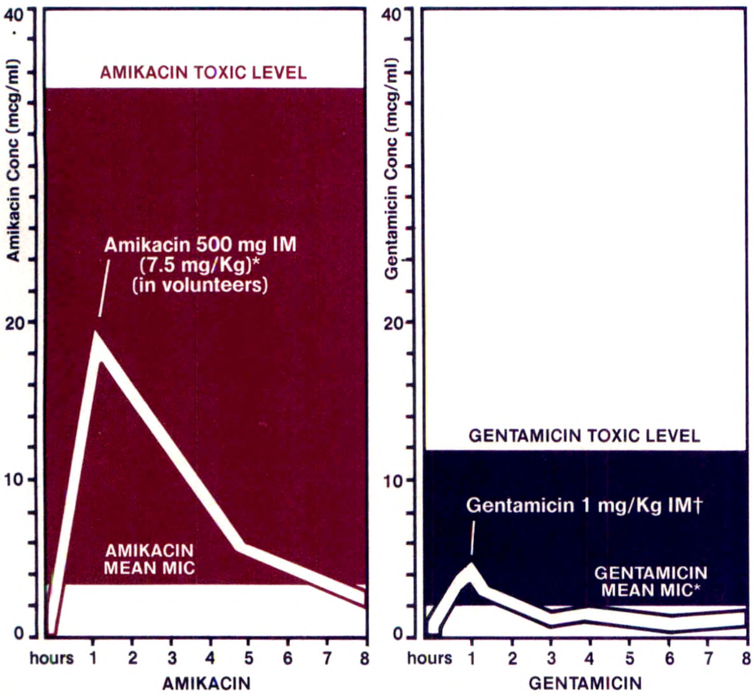

Broader therapeutic index

Amikin's Toxic-to-Therapeutic Index (ratio of toxic serum level to Mean MIC) is three times greater than the next leading aminoglycoside!

Because individual patient serum levels may vary from statistical averages, Amikin's broader margins reduce the risk of subtherapeutic or toxic dosage.

*Data on file, Bristol Laboratories

†Concentration curves adapted from: Winter RE, Litwack KD, Hewitt WL: *J infect Dis* 124 (suppl): 590-595, December 1971

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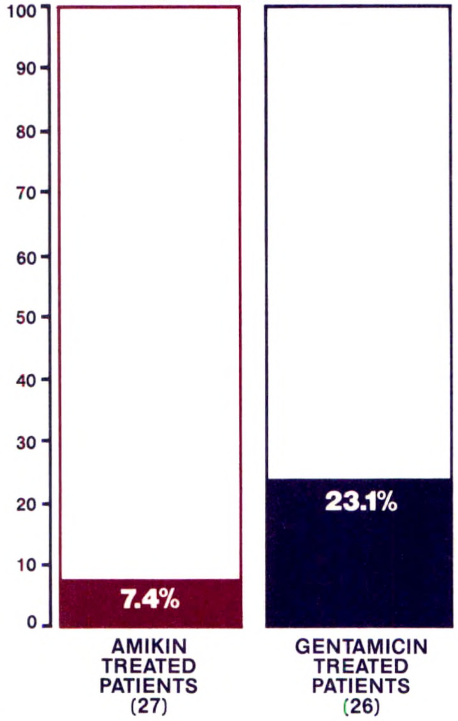
COMPARISON OF OTO- AND NEPHROTOXICITY AS DETECTED BY AUDIOMETRIC & RENAL FUNCTION MONITORING



Well tolerated

As with other aminoglycosides, adverse auditory and renal reactions may occur at higher doses, reversible in some instances. But, in a study comparing the oto- and nephrotoxicity of amikacin and gentamicin among 53 monitored patients, Amikin demonstrated a significantly reduced side effects risk. (Other published studies have shown little or no differences in toxicity).

Special Note: In Amikin clinical trials, hearing loss was rarely clinical and usually an audiogram was needed to identify such a loss. Adverse renal reactions due to Amikin usually consisted of elevations of serum creatinine and/or BUN, which were usually reversible.

Adapted from Lerner SA, Seligsohn R, Rudd R and Matz GJ. Comparative clinical studies of ototoxicity and nephrotoxicity of amikacin and gentamicin. Proceedings 10th International Congress of Chemotherapy, Zurich, Switzerland Sept. 1977.

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AMIKIN® IM IV
AMIKACIN SULFATE

Probably today's most important hospital antibiotic.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
AMIKIN® (amikacin sulfate)
For complete information, consult Official Package Circular. (1) AMIKIN 5/24/76

Warnings:
Patients treated with aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use.

Ototoxicity, both auditory and vestibular, can occur in patients treated at higher doses or for periods longer than those recommended. The risk of amikacin-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing.

The ototoxicity potential of amikacin in infants is not known. Until more safety reports become available, amikacin should be used in infants only in those specific circumstances when susceptibility testing indicates that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed closely for evidence of toxicity.

Aminoglycosides are potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Evidence of impairment in renal, vestibular or auditory function requires discontinuation of the drug or dosage adjustment.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 35 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells and casts.

Concurrent and/or sequential use of topically or systemically neurotoxic or nephrotoxic antibiotics should be avoided.

Amikin should not be given concurrently with potent diuretics.

Usage in Pregnancy: Amikin should be used in pregnant women only when clearly needed.

Indications:
Serious infections due to susceptible strains of Gram-negative bacteria including pseudomonas sp., *E. coli*, indole-positive and indole-negative proteus sp., providencia sp., klebsiella-enterobacter-serratia sp., and acinetobacter sp. Culture and sensitivity studies should be performed.

Clinical studies have shown Amikin to be effective in bacteremia and septicemia (including neonatal sepsis); in serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft-tissue; intra-abdominal infections (including peritonitis); and in burns and post-operative infections (including post-vascular surgery). Clinical studies have shown Amikin (amikacin sulfate) also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Amikin injectable, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

Bacteriologic studies should be performed to identify causative organisms and their susceptibilities to amikacin. Amikin may be considered as initial therapy in suspected Gram-negative infections and therapy may be instituted before obtaining the results of susceptibility testing. Clinical trials demonstrated that Amikin was effective in infections caused by gentamicin and/or tobramycin resistant strains of Gram-negative organisms, particularly *Proteus rettgeri, Providencia stuartii, Serratia marcescens* and *Pseudomonas aeruginosa.* The decision to continue therapy with the drug should be based on results of the susceptibility tests, the severity of the infection, the response of the patient and the important additional considerations contained in the "Warning" box above.

Amikin has also been shown to be effective in staphylococcal infections and may be considered as initial therapy under certain conditions in the treatment of known or suspected staphylococcal disease such as, severe infections where the causative organism may be either a Gram-negative bacterium or a staphylococcus, infections due to susceptible strains of staphylococci in patients allergic to other antibiotics, and in mixed staphylococcal/Gram-negative infections.

Amikacin may be indicated in the treatment of neonatal sepsis when susceptibility testing indicates that other aminoglycosides cannot be used. In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin-type drug may be indicated because of the possibility of infections due to Gram-positive organisms such as streptococci or pneumococci.

Contraindications:
A history of hypersensitivity to amikacin.

Warnings:
See "Warning" box above.

Precautions:
Amikin is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymycin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Adverse Reactions:
Ototoxicity—See "Warning" box.

Nephrotoxicity—Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other—Skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

Dosage and Administration:
The usual I.M. or I.V. dose with normal renal function is 15 mg./Kg./day divided into 2 or 3 equal doses administered at equally-divided intervals. For the heavier individual (greater than 100 Kg.), the total daily dose should not exceed 1.5 Gms. per day.

When amikacin is indicated in newborns (see box "Warning"), it is recommended that a loading dose of 10 mg./Kg. be administered initially to be followed with 7.5 mg./Kg. every 12 hours.

The usual duration of treatment is 7 to 10 days. The total daily dose by all routes of administration should not exceed 15 mg./Kg./day for the average-weight person. In the unusual circumstances where treatment beyond 10 days is considered, the use of Amikin should be reevaluated and, if continued, renal and auditory functions should be monitored daily.

For patients with impaired renal function, whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval.

The solution for intravenous use is prepared by adding the contents of a 500 mg. vial to 200 ml. of sterile diluent such as Normal Saline or 5% Dextrose in Water or any other compatible solution.

The solution is administered over a 30- to 60-minute period.

Supplied:
Rubber-capped vials as a ready-to-use sterile aqueous solution: 100-mg., 500-mg., and 1.0-Gm. vials.

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BRISTOL LABORATORIES
Division of Bristol-Myers Co.
Syracuse, New York 13201

Opsonic α_2 Surface Binding Glycoprotein Therapy During Sepsis

WILLIAM A. SCOVILL, M.D., THOMAS M. SABA, PH.D., FRANK A. BLUMENSTOCK, PH.D.,* HARVEY BERNARD, M.D., SAMUEL R. POWERS, JR., M.D.

From the Departments of Physiology and Surgery,
Albany Medical College of Union University,
Albany, New York

A pronounced depletion of an opsonic protein for hepatic reticuloendothelial (RE) phagocytosis has been demonstrated in critically ill trauma patients. This opsonic α_2 surface binding (SB) glycoprotein has immunologic identity and a similar amino acid composition to cold insoluble globulin (CIg). Since CIg can be concentrated in cryoprecipitate, it was utilized as a readily available source of opsonic α_2SB glycoprotein for replacement therapy after injury with documented hypoopsonemia. Six septic patients (2 multiple trauma, 2 thermal burn, and 2 intra-abdominal abscess) were studied to test whether cryoprecipitate infusion would restore this humoral component. Pre- and posttherapy opsonin levels were determined by bioassay and electroimmunoassay. In all patients, severe opsonin depletion was reversed following cryoprecipitate infusion. All patients had a rapid improvement in febrile state, normalization of leukocyte levels, and improvement in pulmonary function as evidenced by decreasing requirements for end expiratory pressure at lowered levels of inspired oxygen. One patient was studied more extensively and demonstrated an increase in cardiac output, limb blood flow, total body and limb oxygen delivery, total body and limb oxygen consumption and a progressive decrease in pulmonary shunt fraction. Thus, opsonic α_2SB glycoprotein deficiency can be reversed by cryoprecipitate infusion in critically ill septic injured patients. Replacement of this humoral factor may be an important therapeutic modality in prevention of multiple organ failure, but it should be administered only after documentation of hypoopsonemia in traumatized patients.

A MAJOR CONTROL MECHANISM[8,9,10,21–26] for the recognition of abnormal particulates and their subsequent phagocytic ingestion by reticuloendothelial hepatic Kupffer cells and perhaps other macrophages is a humoral factor referred to as opsonic alpha-2-surface binding (SB) glycoprotein (opsonic α_2SB glycoprotein). Recent studies in man have documented a depression of circulating opsonic α_2SB glycoprotein activity by bioassay following multiple trauma and abdominal operation.[29,30] In these studies, nonsurviving trauma patients demonstrated a very profound depletion with no sustained tendency for recovery of normal opsonic glycoprotein levels, whereas surviving patients had spontaneous improvement in the level of this opsonic protein to normal or above normal levels.[29] Furthermore, documented septicemia was consistently associated with depressed levels of this opsonic protein.

In animal studies there is a close correlation between the presence of opsonic activity as manifested by this α_2 glycoprotein and phagocytic clearance of intravenously injected test colloids.[22,26] RE phagocytic depression in animals following injury, including abdominal surgery, blunt trauma, hemorrhagic shock, and burn injury is directly related to the presence in plasma or serum of opsonically active protein.[24,26] Restoration of normal phagocytic clearance capacity has been associated in all cases with a restoration of this humoral mechanism. Indeed, recent studies on the effects of laparotomy in rats reveal a complete circumvention of postoperative phagocytic depression by the intravenous administration of purified rat opsonic α_2SB glycoprotein.[21]

Purification of human opsonic α_2SB glycoprotein in our laboratory has led to both its biochemical characterization as well as the development of an immunoassay for quantification of its serum level.[8,9,10] Biochemical characterization reveals that it is a large molecular weight glycoprotein with an amino acid composition and immunologic similarity to human cold-insoluble globulin (CIg) or so-called plasma fibronectin.[10,20] While replacement therapy in small animals has been recently demonstrated, one of the major factors limiting replacement of opsonic deficiency in patients following trauma and burn has been the availability of the protein in sufficiently large sterile quantities. However, the common identity of cold-insoluble

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

* NSRA Postdoctoral Trauma Fellow in the Department of Physiology, Albany Medical College, supported by T32-GM-07033 from the Institute of General Medical Sciences.

Supported by a Department of Physiology Grant GM-21447 from the National Institute of General Medical Sciences.

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globulin and the opsonic α_2SB glycoprotein suggests that opsonin therapy in patients may be possible by utilization of human plasma cryoprecipitate. In the present study, we tested the hypothesis that cryoprecipitate infusion into septic surgical, burn, and trauma patients would be an effective means of correcting opsonic deficiency as tested by both bioassay and immunoassay.

Methods and Patients Studied

A total of six patients were studied. Two patients had suffered multiple trauma; two patients had major operations for intra-abdominal abscess; and two patients had sustained major thermal burn amounting to either 60 or 75% body surface area. All patients at the time of study had either documented or suspected septicemia, and all had abscess or invasive wound infection. The response to cryoprecipitate therapy was assessed in all patients by the usual clinical criteria. These criteria consisted of pulse rate, temperature, leukocyte count, and mental alertness. Extensive evaluation of pulmonary and cardiovascular hemodynamic endices was done in one of these patients admitted to the Albany Trauma Center. Cryoprecipitate, obtained from ten units of fresh plasma and suspended in a volume of 250 ml, was infused intravenously over a 60 minute period. Circulating levels of opsonic α_2SB glycoprotein was assessed by bioassay (liver slice) and immunoassay (rocket immunoelectrophoresis) prior to infusion and at 0.5, 4, 24 and 48 hours following cryoprecipitate infusion.

Opsonic activity of serum was assessed in terms of its ability to support *in vitro* hepatic Kupffer phagocytosis of test particles.[11,14,15,23,25] In this procedure, liver slices weighing 200–400 mg were prepared from normal rat donors with a Stadie-Riggs tissue slicer. The slices were incubated in a medium containing 1 ml of the experimental human serum, 2 ml of Krebs-Ringer phosphate (pH 7.4), 100 USP units of heparin, and 2 mg of the gelatinized ^{131}I labelled RE test lipid emulsion. This gelatinized RE test lipid emulsion has been previously described and its exclusive uptake by phagocytic cells of the RE system has been documented by light and electron microscopic techniques. All samples were incubated with oscillation in a 25 ml Erlenmeyer flasks under a gas phase of 95% O_2 and 5% CO_2 in a Dubnoff metabolic shaker at 37° for 30 minutes. Following incubation, the liver slices were washed, weighed, and isotopically analyzed for colloid uptake. Opsonic activity was expressed as percentage of the injected 2000 μg colloid dose (ID) phagocytized per 100 mg of liver slice (%ID/100 mg).

Immunoreactive opsonic α_2SB glycoprotein levels were quantitated by electroimmunoassay as recently described by our laboratory.[8,9] The human opsonic protein was isolated by a combination of ammonium sulfate fractionation, high voltage free-flow electrophoresis, and gel filtration on Sepharose 4B as recently described.[9,10] Purity was tested by both gradient polyacrylamide gel electrophoresis and electroimmunoassay using polyspecific antiserum. Antiserum to the isolated opsonic protein was prepared as previously documented.[9] When antiserum is not monospecific, it can be rendered monospecific by absorption with glutaraldehyde cross-linked opsonin depleted human serum accomplished by particle absorption. The monospecific antiserum was then mixed with a 1% agarose gel to yield a final antiserum concentration of 0.6% for use in the electroimmunoassay. Three millimeter wells were cut in agarose coated 5 × 10 inch glass plates at intervals of 1 cm, and 10 μl of diluted 10% experimental serum was added to each well. Samples were electrophoresed toward the anode at a voltage of 7V/cm at 4° for 22 hours. The plates were then stained and washed as previously described.[9] The human serum standard for the assay contained 400 μg/ml of immunoreactive human opsonin. Rocket heights were recorded in millimeters and a double reciprocal standard plot (1/mm versus 1/μg opsonin) was defined with a DEC-10 computer using the standard serum at concentrations of 2–20% to allow for determination of immunoreactive protein in μg/ml.[8]

Arterial P_{O_2}, P_{CO_2} and pH were measured using standard electrodes, calibrated with gases assayed by the micro-Scholander technique. Arterial and mixed venous samples were drawn simultaneously and the physiological shunt fraction was calculated using Berggren's shunt formula[6] at the patients therapeutic level of inspired oxygen fraction (FIO_2). For the determination of physiological dead space, expired gas was mixed in a stirring chamber from which a sample was pumped directly into the blood gas analyzer. Mixed expired gas was assayed for CO_2 and O_2 simultaneously with the sampling of arterial and mixed venous blood for blood gas determinations. The physiological dead space/tidal volume ratio (V_D/V_T) was calculated using the Suwa and Bendixen modifications of the equations of Enghoff and Bohr.[31]

Blood flow to a segment of the leg was measured by venous occlusion impedance plethysmography.[34] A tetrapolar impedance plethysmograph measured electrical impedance of the limb segment at 100 KHz. A blood pressure cuff located proximal to the segment was inflated to a pressure sufficient to occlude venous outflow. The limb segment then increased its volume for several seconds due to the continuing arterial inflow. This volume increase results in an impedance decrease, allowing an indirect quantitative measurement of arterial inflow. Limb blood flow in ml/min/100 gm after occlusion of venous outflow is calculated by:

$$\text{Flow} = \rho \frac{L^2}{Z_0^2} \times \frac{\Delta Z}{\Delta T}$$

where: ρ = resistivity of the limb tissue assumed to equal 150 ohm cm.
L = the distance between the measuring electrodes in cm.
Z_0 = the total impedance between the measuring electrodes in ohms.
$\Delta Z/\Delta T$ = the change in impedance over time following venous occlusion in ohm/min.

Whole body O_2 consumption ($\dot{V}_{O_2}$) was measured by the direct Fick technique. Oxygen content of arterial and mixed venous blood samples was calculated from the hemoglobin concentration determined spectrophotometrically, and the oxyhemoglobin saturation determined by blood gas slide rule.[28] Cardiac output was determined by dye dilution.

Limb V_{O_2} was determined by analyzing femoral venous and arterial blood samples for their O_2 content and multiplying by limb blood flow obtained by venous occlusion plethysmography.

Case Reports

Case 1. This 66-year-old woman developed lower abdominal pain and fever and gram negative septicemia. Exploratory laparotomy revealed a large pelvic abscess with suspected perforated

TABLE 1. *Clinical Course Before and After Intravenous Cryoprecipitate Therapy in Septic Surgical, Trauma and Burn Patients*

Patient Number	Clinical Parameters* 48 Hr Period Pretherapy	Clinical Parameters* 48 Hr Period Posttherapy
1	Large pelvic abscess with colocutaneous fistula; persistent sepsis. Temperature = 37.9–39.5° Pulse = 88–122/min WBC = 2,700–3,300/mm^3	Rapid recovery, no antibiotics needed. Temperature = 36.6–37.2° Pulse = 80–100/min WBC = 4,200–4,700/mm^3
2	Traumatic wound of lower extremity; High above-knee amputation; Confused and disoriented; Co-existent sepsis and pulmonary insufficiency. Temperature = 39.5–40.7° Pulse = 130–160/min WBC = 11,600–37,900/mm^3 Pao$_2$ = 88 torr on 10 cm H$_2$O PEEP and 50% FIO$_2$	Improved mental status and pulmonary function. Temperature = 37.9–38.8° Pulse = 88–100/min WBC = 13,000–16,500/mm^3 Pao$_2$ = 74 torr on 5 cm H$_2$O PEEP and 50% FIO$_2$
3	Multiple trauma; left pleural emphyema; Confused and disoriented; Pulmonary insufficiency; Serratia marcescens cultured from pleural space, urine, and sputum. Temperature = 37.2–38.8° Pulse = 93–130/min WBC = 18,500–22,800/mm^3 Pao$_2$ = 53 torr on 5 cm H$_2$O PEEP and 40% FIO$_2$	Improved mental state and pulmonary function. Temperature = 37.2–37.9° Pulse = 80–110/min WBC = 16,600–17,400/mm^3 Pao$_2$ = 117 torr on 5 cm H$_2$O PEEP and 40% FIO$_2$
4	Flame burns involving 75% of body surface; positive blood cultures. Temperature = 37.9–39.5° Pulse = 100–140/min WBC = 6,700–9,200/mm^3 Pao$_2$ = 58 torr on 0 cm H$_2$O PEEP and 60% FIO$_2$	Improvement in mental status. Temperature = 35.5–37.5° Pulse = 86–104/min WBC = 5,400–6,500/mm^3 Pao$_2$ = 115 torr on 5 cm H$_2$O PEEP and 40% FIO$_2$
5	Burn involving 60% of body surface; blood cultures positive. Temperature = 39–39.5° Pulse = 118–160/min WBC = 10,000–16,700/mm^3 Pao$_2$ = 58 torr on 0 cm H$_2$O PEEP and 40% FIO$_2$	Improved pulmonary function. Temperature = 36–38.6° Pulse = 110–128/min WBC = 6,500–8,800/mm^3 Pao$_2$ = 128 torr on 0 cm H$_2$O PEEP and 40% FIO$_2$
6	Multiple trauma; Delayed massive intra-abdominal hemorrhage; Jaundiced and septic 3 weeks post-injury. Temperature = 37.2–39.5° Pulse = 100–132/min WBC = 23,000–39,500/mm^3 Pao$_2$ = 130.5 torr on 12 cm H$_2$O PEEP and 45% FIO$_2$	Improved cardiac and peripheral hemodynamics (Table 2). Temperature = 37.2–39.5° Pulse = 78–140/min WBC = 8,000–39,300/mm^3 Pao$_2$ = 137.9 torr on 12 cm H$_2$O PEEP and 45% FIO$_2$

* Values are presented as range of multiple determinations done over 48 hr period before and 48 hr period after therapy.

appendicitis. After appendectomy and drainage of the pelvic abscess, she developed upper gastrointestinal bleeding and required transfusion. Subsequently, an enterocutaneous fistula was identified and four weeks following her first operation, she was transferred to the Albany Medical Center. The cutaneous fistula was identified by sinogram to originate from the sigmoid colon. At this time, the patient showed signs of sepsis with tachycardia, spiking fever, and leukopenia. At operation, a pelvic abscess was drained and a diverting colostomy created with closure of the sigmoid fistula. Cryoprecipitate was transfused intraoperatively. The combination of cryoprecipitate infusion and drainage of her abscess, was followed by an improvement of fever and white count (Table 1). While multiple antibiotics had been used prior to her transfer and operation, no further antimicrobial therapy was given.

Case 2. This 20-year-old man was involved in a vehicular accident resulting in mild cerebral contusion and injuries to his right lower extremity consisting of fractures and extensive soft tissue injury with devitalized skin flaps. Hematuria was present with a normal intravenous pyelogram. In spite of debridement of the lower extremity, he became septic with deterioration in the appearance of the soft tissues of his leg during the first 36 hours following his injury. He was then transferred to Albany Medical Center where smears of the wound demonstrated pleomorphic rods, gram positive rods, and gram positive cocci. He manifested a high fever, marked tachycardia, tachypnea, and severe hypoxia requiring ventilatory support. Debridement of his wounds revealed myonecrosis and an above the knee amputation was performed. Preoperatively, he had been treated with high dose penicillin and tobramycin and this was continued postoperatively. On the first postoperative day, his febrile course and severe respiratory insufficiency persisted with subcutaneous emphysema and erythema noted over the anterior chest wall. Cryoprecipitate therapy was initiated on the second day after operation. Within 24 hours, the patient's pulmonary function and hyperpyrexia improved and he became more alert and responsive (Table 1). A steady modest temperature elevation persisted until eventual closure of the amputation stump.

Case 3. This 58-year-old man was involved in a vehicular accident and sustained a fracture dislocation of left hip, fractured left ulna and left tibia, multiple fractured ribs resulting in a flail segment and bilateral pneumothorax. There was evidence of lung contusion on x-ray within the first 24 hours after injury. Exploratory laparotomy revealed a stellate laceration of the right lobe of his liver and hematoma in the region of the duodenum and pancreas. During the first 24 hours after surgery there was a rapid deterioration of his pulmonary function and he was transferred to the Albany Medical Center. Severe respiratory insufficiency persisted for the first several weeks following injury and this was complicated by a large intrapleural air leak. Mild renal failure developed with creatinine clearance as low as 25 ml/min with oliguria. Four weeks following injury a left pleural empyema was identified and drained. Serratia marcescens was subsequently cultured from the left pleural space, urine and sputum. The patient developed tachycardia, fever, leukocytosis, and persistent respiratory insufficiency. He was treated with cryoprecipitate and during a two day period following treatment, the febrile course and sensorium all improved with relief of the persistent pulmonary insufficiency (Table 1). By the fourth day mechanical ventilatory support was no longer required.

Case 4. This 64-year-old man sustained a 75% body surface burn, 70% full thickness, and evidence of smoke inhalation. He had five documented episodes of septicemia. During these periods he had positive blood cultures, marked alteration in his febrile state, leukocytosis, as well as other signs of sepsis including depressed mental function and failure to accept nasogastric tube feedings. He was dependent upon mechanical ventilation throughout most of his hospital course and his pulmonary function further deteriorated with septic episodes. On two separate occasions, he was treated with cryoprecipitate obtained from 10 units of blood. Following each course of cryoprecipitate therapy, there has been an improvement in the clinical signs of sepsis, pulmonary function and no growth obtained on blood cultures. The patient has completely healed 22 weeks following burn injury.

Case 5. This 52-year-old white woman sustained a 60% flame burn, all full thickness, while lighting a gas stove. She expired eight weeks following her burn injury and during the course of her hospitalization, she had four documented episodes of septicemia. The first episode occurred three weeks following burn injury where blood cultures were repeatedly positive for staphylococcus aureus coagulase positive. At that time, she had hyperpyrexia, intestinal ileus and depressed mental status. After treatment with cryoprecipitate, her temperature decreased, mental status improved, and an improvement in her pulmonary function was observed (Table 1). Later in the course of her illness, she presented a clinical picture compatible with fungal septicemia and eventually succumbed.

Case 6. This 30-year-old man sustained splenic rupture, pelvic fracture, and multiple lacerations as a result of a vehicular accident. In the early postoperative period following splenectomy he became febrile, hypoxic, and required ventilatory support. During a ten day period the fever persisted and hepatic function deteriorated with resulting jaundice. He developed right upper quadrant pain and then hypotension. Exploratory laparotomy revealed a suprahepatic hematoma which was evaluated. No bacteria were subsequently cultured from the hematoma. Eight hours following this operation, the patient was profoundly hypotensive with evidence of massive intra-abdominal hemorrhage. Immediate reoperation revealed bleeding from the celiac axis at the origin of the splenic artery which was ligated. The patient had a cardiac arrest and multiple transfusions were required for resuscitation. There was evidence of dilutional coagulopathy and following this operation, there was extensive hemorrhage from the wound requiring reoperation for control of bleeding. Following these operations, he was admitted to the Trauma Center for further care and study. He developed acute renal failure, followed by spontaneous diuresis and restoration of renal function. His mental function was markedly depressed and his electroencephalogram grossly abnormal. The febrile course persisted with leukocytosis and four weeks following his initial injury blood cultures were positive for *Klebsiella pneumoniae*. This organism was also cultured from the abdominal wound. The white blood count was 39,000 cells/mm^3 and his temperature markedly elevated. Infusion of cryoprecipitate was followed by improvement in his fever, reduction in leukocyte count, as well as the transient but striking pulmonary and cardiovascular improvements as presented in Table 2. His mental status did not improve, and the electroencephalogram reflected brain death. He expired eight weeks following his initial injuries.

Results

The quantification of opsonic α_2SB glycoprotein in plasma cryoprecipitate utilized for intravenous therapy is presented in Figure 1, as detected by electroimmunoassay. The concentration of the protein in normal human serum is usually about 330–360 μg/ml, and an approximate 10–12 fold concentration (4.0 mg/ml) of the protein was routinely detected in plasma cryoprecipitate. In the present study, each of the septic patients was infused intravenously with 250 ml of plasma cryoprecipitate over a 60 minutes interval which provided about 1.0 g of opsonic protein per patient.

TABLE 2. *Cardiovascular and Pulmonary Response to Intravenous Cryoprecipitate Therapy in Multiple Trauma Patient Over a 72 Hour Posttherapy Period*

Parameter	Pretherapy	Time After Intravenous Infusion 4 Hr	24 Hr	48 Hr	72 Hr
Pa_{O_2} (mm Hg)	131	126	130	156	99
Physiological Shunt (%)	14.2	12.9	10.5	8.8	6.8
Dead Space (V_D/V_T)	0.377	0.438	0.444	0.475	0.345
Cardiac Output (L/min)	6.97	9.00	6.85	7.90	5.74
Cardiac Index (L/min/sq. m)	3.30	4.27	3.25	3.74	2.72
Total Body O_2 Delivery (ml/min)	1030	1667	995	1203	795
Total Body O_2 Consumption (ml/min)	210	600	273	290	161
Limb Blood Flow (ml/min/100 g tissue)	3.80	10.6	1.49	1.36	2.81
Limb O_2 Delivery (ml/min/100 g tissue)	0.562	1.628	0.216	0.206	0.389
Limb O_2 Consumption (ml/min/100 g tissue)	0.084	0.249	0.053	0.050	0.072
Mixed Venous Saturation (%)	79.6	76.6	72.7	76.8	81.8
Mixed Venous P_{O_2} (mm Hg)	47.2	45.1	41.8	41.0	44.6

All data points were obtained at identical ventilator settings: FI_{O_2} = 45%; PEEP = 13 cm H_2O.

Both immunoreactive and bioassayable levels of opsonic α_2SB glycoprotein over a 48 hour period following intravenous cryoprecipitate infusion are presented in Figure 2. There was a simultaneous elevation in both bioassayable serum opsonic activity ($p < 0.05$) and serum immunoreactive opsonic α_2SB glycoprotein ($p < 0.05$) at the ½ and 4 hr interval with return to pretherapy levels by 24–48 hours following cryoprecipitate infusion. The percentage increment in immunoreactive protein was much less than the associated elevation in bioassayable activity as tested by the liver slice assay in each corresponding test sample. For example, the 30–50% elevation in immunoreactive protein which was detected over the 0.5–4.0 hour period, corresponds to an approximate 150% increase in bioassayable activity (Fig. 3). This finding suggests that the *in vivo* functional state of the RES may have been substantially stimulated at the cryoprecipitate dose utilized in these preliminary studies.

The clinical responses in terms of temperature, heart rate, white cell level, and pulmonary function including ventilatory requirements are presented in Table 1. In general, the patients as a group manifested a drop in temperature, normalization of their leukocyte level, improvement in pulmonary function and acute reversal of their septic state early after cryoprecipitate infusion. In an attempt to more critically analyze the responsiveness of these patients to cryoprecipitate, one patient was extensively studied in the Trauma Center with respect to pulmonary function, cardiac performance, and peripheral circulatory hemodynamics (Table 2). In this patient, there was an increase in cardiac output, total body O_2 delivery and O_2 consumption, limb blood flow, as well as limb O_2 delivery and O_2 consumption which was apparent over the early posttherapy period and returned toward base-line by 24 hours. This response during the early posttherapy intervals occurred in association with the elevation of immunoreactive and bioreactive opsonic protein. In contrast to the transient nature of the response relative to cardiac output and limb blood flow, a progressive decline in pulmonary shunt fraction was observed over the three day period.

Discussion

Participation of the reticuloendothelial system in resistance to shock and trauma is not a new concept.[24,33] Hepatic phagocytic depression following hemorrhage, trauma, surgery, and thermal burn has been documented in both animals and man and RE function has been suggested to be of importance to survival following

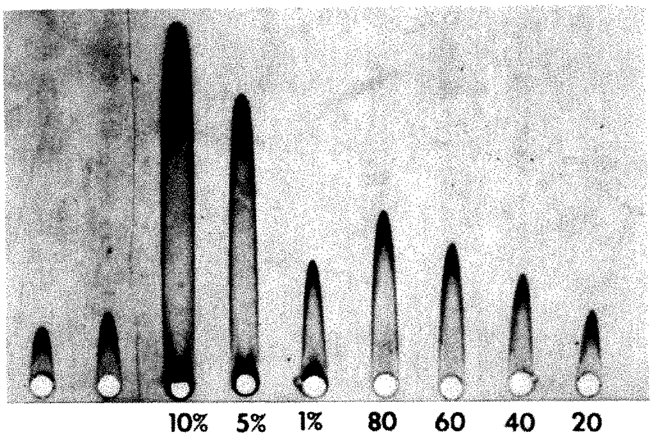

FIG. 1. Immunologic detection of opsonic α_2SB glycoprotein in fresh human plasma cryoprecipitate with the use of rocket immunoelectrophoresis (electroimmunoassay). Each well contained a 10 μl aliquot of either a 1, 5 or 10% dilution of cryoprecipitate. Rocket height was compared to varying quantities of the purified human protein. Isolated protein solutions had an opsonin concentration of either 20, 40, 60, or 80 μg/ml and a 10 μl aliquot of each was tested. Cryoprecipitate typically has an opsonic protein concentration of approximately 4 mg/ml and each patient received 250 ml (about 1.0 g) intravenously over a 60 minutes infusion interval. Percentages refer to cryoprecipitate, numbers refer to μg/ml α_2SB glycoprotein.

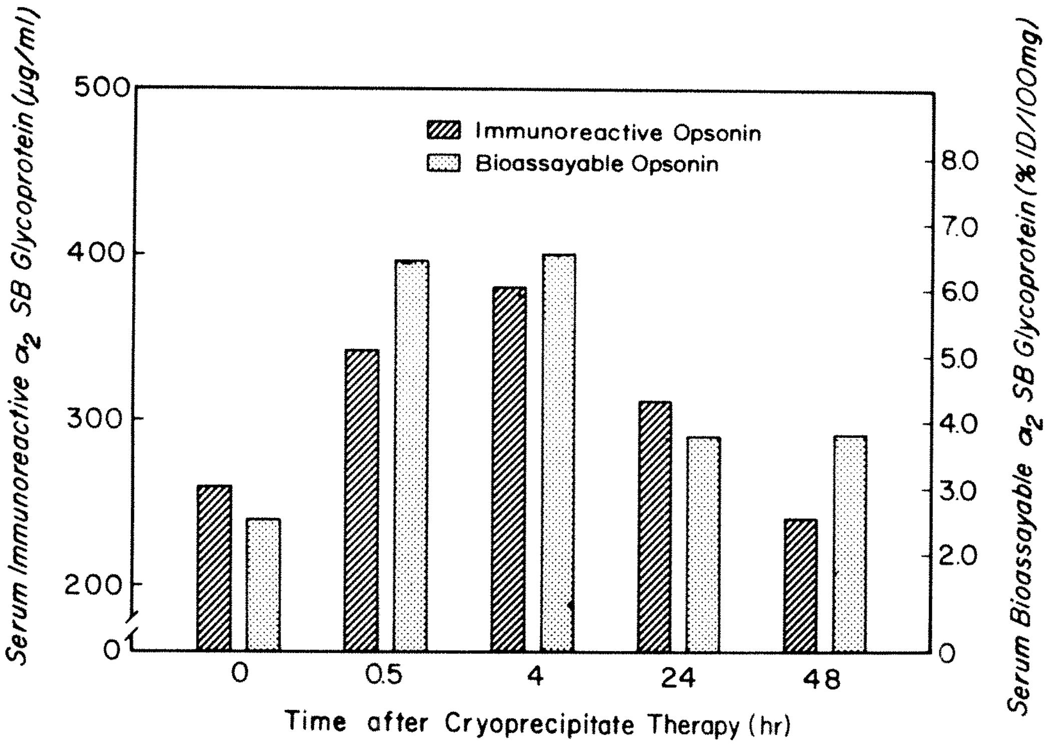

FIG. 2. Temporal response in septicemic patients after cryoprecipitate infusion. Average bioassayable serum opsonin activity and immunoreactive serum opsonic α_2SB glycoprotein concentration prior to and over a 48 hour period after cryoprecipitate infusion. Values presented are the mean of determinations in the six patients. Bioassayable opsonic activity is expressed as per cent of the added 2000 µg colloid dose phagocytized per 100 mg liver tissue. Serum immunoreactive protein is expressed as µg/ml.

major injury.[3,15,24,26,29,30] Many studies dealing with host resistance to sepsis after burn and trauma have emphasized granulocyte function[1,2] as influenced by specific opsonic immunoglobulins and complement in addition to disruption of the immune response. For example, Alexander et al.[1,2] has proposed that phagocytic dysfunction of granulocytes due to opsonic deficiency may be a limiting factor in antibacterial immunity in the septic burn and trauma patient. Thus, the combined functional capability of the polymorphonuclear leukocyte, the blood monocytes, and fixed cells of the reticuloendothelial system[22] may collectively represent a broad-based cellular defense system where levels of relative importance would be dependent on the type of injury and the site or extent of infection.

A noninvasive method to quantify the functional capability of the RES in the clinical setting has yet to be developed. The *in vivo* colloid clearance technique is invasive and its routine applicability for patient studies is limited[22] since colloid injection leads to opsonic α_2SB glycoprotein depletion[8,22,25] and can be correlated with increased sensitivity to various forms of trauma and injury in addition to lowering antibacterial immune defenses.[22,26] Thus, sequential assessment of RE function by colloid clearance has inherent problems in terms of routine clinical applicability. Since opsonic α_2SB glycoprotein activity relates closely to liver phagocytic activity,[15,17,22,25,26] the bioassay[23,25] as well as the immunoassay[8,9] of α_2SB glycoprotein may be a noninvasive index of the functional state of the RES.

Methods to modulate RE function or reverse RE depression in the trauma patient have not been reported. While a variety of chemical and nonspecific immunostimulants are available which can increase liver and spleen phagocytic activity, these agents are not of value for widespread clinical utilization due, in part, to the hypertrophy and hyperplasia of the RE system that is induced.[22] The present data suggests that intravenous administration of opsonic α_2SB glycoprotein, accomplished by cryoprecipitate infusion, may be a selective means to correct opsonic deficiency and augment RE function. Further technical modifications with eventual utilization of purified sterile isolated human opsonic protein[9] in a biologically active form will be an important advancement. Recent development of an affinity chromatographic technique in our laboratory has led to the potential for a rapid and selective means to isolate this protein to antigenic purity (Blumenstock and Saba, unpublished data). This was previously achieved by a combination of ammonium sulfate fractionation, high voltage free-flow electrophoresis, and gel filtration.[8-10]

Our demonstration[9,10] that opsonic α_2SB glycoprotein is similar to cold-insoluble globulin or plasma fibronectin is supported by several observations[20] and is of major biological significance. Both proteins have a molecular weight of about 450,000 daltons and consist of two subunits, each of about 220,000–230,000 daltons held together by disulfide bonds.[10] Both proteins have a similar amino acid composition and Ouchterlony double diffusion demonstrates their antigenic identity utilizing monospecific antiserum to each respective protein.[10] Cold-insoluble globulin has a high affinity for binding to exposed collagen and injured tissue and nonspecific consumption at sites of tissue injury or areas of ischemia following trauma and shock may be etiologic in its depletion after trauma.[16,20] In addition, potential activation of intravascular coagulation following trauma[7] with the generation of microaggregates of fibrin and injured platelets within the vascular compartment would represent a phagocytic load to the RES resulting in opsonic deficiency.[24] This deficiency may be magnified during septicemia in which circulating immune complexes as well as free bacteria can provide an additional particulate load to the liver and spleen. Previous findings of opsonic α_2SB glycoprotein deficiency in septic trauma patients[29] coupled with the observed association of sepsis and multiple organ failure[12,37] following injury have led us to the hypothesis[24] that RE dysfunction mediated by opsonic deficiency may be a major factor in the etiology of multiple organ failure following trauma.

Recent studies[29,30] in traumatized man are consistent with our animal data.[20] Spontaneous restoration of normal levels of opsonic α_2SB glycoprotein in man after trauma has been associated with survival.[29] In the present study we have augmented circulating opsonic α_2SB glycoprotein levels by the infusion of cryoprecipitate. All patients demonstrated a transient clinical improvement in pulmonary function and a lessening of the septic state following a single therapeutic trial of cryoprecipitate which closely corresponded to the transient reversal of the opsonic deficiency. These preliminary observations of clinical improvement are in agreement with animal data[17,21] but will require more extensive evaluation by a controlled prospective study. The consequences of maintaining a heightened serum level of this protein for a prolonged period of time remains to be determined, but is presently under investigation.

One patient, who was studied in more detail in the Trauma Center, demonstrated substantial increase in cardiac output as well as a decrease in pulmonary shunt fraction with improved limb blood flow and an increase in total body as well as limb oxygen consumption. While the mechanism responsible for the increased cardiac output remains to be determined, one might hypothesize that this may be related to increased Kupffer cell clearance of noxious particulates which may influence cardiac performance. The volume of cryoprecipitate infused and its total protein content would not be expected to increase cardiac output to the degree observed. Particulate localization in peripheral microcirculatory beds may also influence capillary permeability, and regional regulation of perfusion. Enhanced limb and total body oxygen consumption following the infusion of cryoprecipitate as documented in the present studies provides some support for these theoretical considerations, and may reflect hepatic RE "protection" of the periphery.[15,22–24]

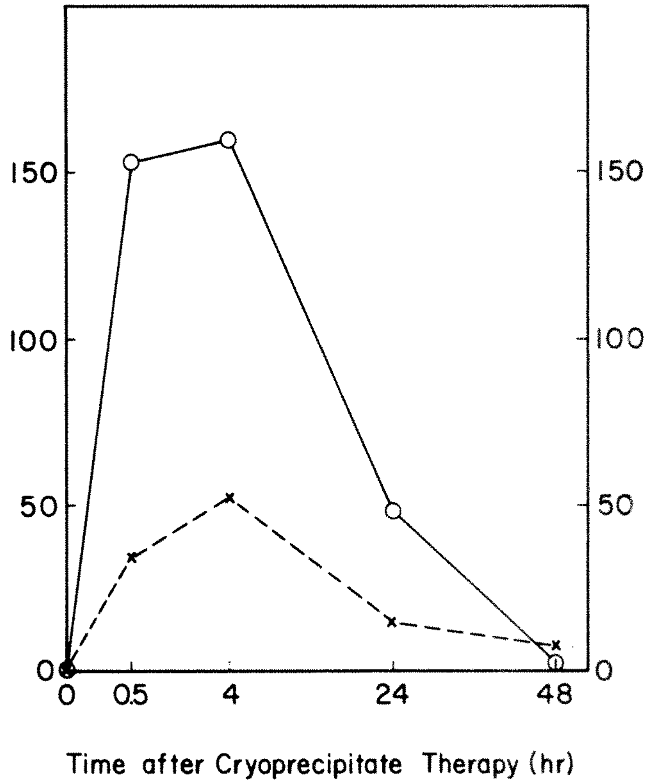

FIG. 3. Quantitative relationship between the posttherapy elevation in immunoreactive opsonic α_2SB glycoprotein as determined by electroimmunoassay and the parallel alteration in bioassayable opsonic activity of serum as tested by *in vitro* liver slice assay using the gelatinized I^{131} RE test lipid emulsion. Values represent the average response in the six patients. Data are expressed as per cent increase observed in each patient from pretherapy values over a 48 hour period after cryoprecipitate administration. Immunoreactive and bioassayable levels were significantly elevated at 0.5 hour ($p < 0.05$) and four hour ($p < 0.05$) but within normal ranges at 24 and 48 hr. ○ —— ○: per cent increase in serum bioassayable Kupffer cell *in vitro* activity. × - - - ×: per cent in serum immunoreactive opsonic α_2SB glycoprotein in patients.

Pulmonary function in the postinjury state may be influenced by the functional integrity of hepatic RE clearance mechanisms.[27] RE phagocytic depression has been shown to result in increased localization of blood-borne particulate matter in the lungs.[15,23] Such microembolization may be etiologic in ventilation–perfusion imbalances, increased pulmonary vascular permeability, and the genesis of pulmonary edema. The close correlation of sepsis with posttraumatic pulmonary insufficiency[12,32] in the trauma and burn patient may be, in part, mediated by the impaired RES removal of circulating microaggregates and immune complexes and their subsequent deleterious influence on lung function and peripheral circulatory perfusion.[4,5,7,19,26] Circulating immune complexes are known to be cleared by RE cells, and complement or endotoxin induced leukostasis within the pulmonary vasculature during sepsis may directly disturb the pulmonary microvasculature as well as increase pulmonary capillary permeability leading to permeability edema. Additionally, the septic or endotoxemic state will not only lead to leukostasis and the formation of immune complexes, but this state itself is a potent activator of intravascular coagulation. Phagocytic clearance of products of coagulation such as altered platelets, fibrin, and other activated coagulation factors has been documented.[13,18] Hepatic Kupffer cells have been shown by immunofluorescence to contain fibrin microaggregates[18] following low-grade intravascular coagulation and Kupffer cell clearance of radiolabelled fibrin has been demonstrated.[13] Furthermore, evidence has been provided that the clearance of fibrin degradation products and fibrinogen-fibrin complexes is related to the functional status of the RES.

The findings of this study document the effectiveness of cryoprecipitate infusion as a means to reverse opsonic α_2SB glycoprotein deficiency in critically ill patients. The data further suggest that the maintenance of normal levels of this humoral component, which would augment RES function, may provide an important means of prevention or attenuation of multiple organ system failure in the critically ill, septic, burn or trauma patient.[20]

Acknowledgments

The authors acknowledge the technical assistance of Miss Vera Gray and Mr. Eshin Cho. The secretarial assistance of Ms. Maryhelen Johnson and Ms. Maureen Kaiser is appreciated. Use of the Albany Trauma Center (GM-15426) and the Albany Medical Center Hospital Burn Unit is acknowledged.

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DISCUSSION

DR. LLOYD D. MACLEAN (Montreal, Quebec): This is a remarkable paper, I think, about a naturally-occurring immune regulatory molecule. It's remarkable for several reasons.

First of all, they have showed a stimulatory effect, whereas most of us working in this field have been able to detect only inhibitors.

They have two quantitative assays, and one of those requires that they purify the opsonic protein, which they have done. Any one of these things, I think, would be enough for a complete discussion.

They have also found a concentrated source for the material, in the form of cryoprecipitate. Finally, they have applied it clinically.

I'd like to show two or three slides, just to put it in perspective, maybe, for some who aren't as familiar with these things.

(Slide) The inflammatory response, the component that they're studying, is over on this side. Opsonic activity is buttering up bacteria, or other particles, so they become attractive to the phagocytes. The Kupffer cell is the particular phagocyte that they're studying.

Several people are working on this side, in chemotaxis. There's a good quantitative assay for intracellular killing. This activity can be quantitated. There isn't too much work going on in here. I'd like to show you two or three slides of activity on this side of the scale.

(Slide) Using this quantitative assay, neutrophils can be taken from trauma patients, put in this grid with this attractant below it and the degree of migration can be accurately quantitated of the neutrophils across this grid.

(Slide) Patients who have been traumatized fall into three groups, generally: a group with minor injuries, who have normal skin tests and don't migrate from the normal range; patients with multiple injuries, two body cavity injuries, with, again, a normal skin test, and finally, people with severe multiple injuries, who have abnormal skin testing, and take about a month to get back to normal.

It looks like this measurement, chemotaxis, (slide) might be a more sensitive index of decreased host resistance than is skin testing.

Finally, as was done here in 14 anergic patients, if one follows them long enough, until they do return, as the skin test returns to normal, so does the chemotaxis. Furthermore, if one takes cells from a normal person and adds the abnormal serum from these anergic patients, those cells will also fail to migrate normally.

I have two or three questions that they might like to speculate on. I'd like to know if they did skin testing on these patients, or others, and if they found this to be helpful. What is the normal response to infection with the opsonic protein? Does a normal person with a controlled infection get a jump in that protein?

I think you did tell us some of the hemodynamic effects, but I'd be interested to know whether in the normal setting, this opsonic protein has a hemodynamic effect.

DR. BEN EISEMAN (Denver, Colorado): I was privileged to review this manuscript in advance. This work is important not because following administration of some plasma fraction several sick septic patients got better. Indeed each had good surgical care and some probably would have otherwise recovered. What is important is the authors' evidence that the glycoprotein fraction, which happily can be isolated relatively easily in the cold precipitated fraction of normal serum, increases opsonization. This is a modern return to a bacteriologic principle whose time, I judge, now has returned.

(Slide) Let me put this in context with our own studies, which for several years have emphasized the etiologic role of remote bacterial sepsis to liver, lung, kidney failure and stress ulcer.

(Slide) Our hypothesis is that such infection produces circulating immune complexes of antigen, antibody and complement and that these particles, if sufficiently large, are caught in the reticular endothelial cells of the liver. If they are smaller than 11S or if the RE cells are saturated or damaged, the complexes slip by the Kupffer cells and land in the lung, kidney or other organs where they cause cellular damage (slide).

This was our hypothesis, and we have evidence that we are correct. In four patients in multiple organ failure and in over 25 rabbits made septic by experimental intraperitoneal abscesses, the immune complexes visualized by immunofluorescent antibodies coating the vasculature of the liver, lungs and kidney in a pattern so far recognized only in glomerular basement membrane disease support the concept presented today that an immune mechanism contributes to organ damage during remote sepsis. The unanswered question remains: How does the opsonin described by the Albany group work?

DR. WILLIAM SCOVILL (Closing discussion): Dr. MacLean, we have not done skin testing in any of these patients, and I think the results of skin testing would have a lot of complex interpretations, which may have very important bearings on future lines of investigation. I think that would be an ideal thing to do.

The questions about opsonic protein levels—that is, the opsonin required for normal Kupffer cell phagocytic function and the influence of infection on these opsonic protein levels—is an important one. There is a suggestion that early infection may result in heightened levels of this opsonic protein, whereas the data I presented in severely traumatized man with documented septicemia, indicated that there was a severe undermining of this opsonic system.

The hemodynamic effects, as I presented in a preliminary fashion in these two patients, are probably not due to the volume of cryoprecipitate infused, since it was so small. It would be appealing to hypothesize an improvement in peripheral microcirculation as a means of improving overall dynamics by the phagocytic ingestion of potentially noxious particulates that are circulating during septic periods.

Dr. Eiseman, we have looked at the question of complement early on, in cruder isolated protein fractions, and have not found complement activity in the crude fractions; and you're quite right, the structure of this protein is not compatible with this being complement.

The further question of what happens to liver blood flow, hepatic sinusoidal blood flow, following the ingestion of a large particulate load is a very interesting one, and one that we have not yet confronted. I think the former model of reticuloendothelial blockade, that induced by large volume colloid injections, was thought at one time to be due to a saturation of the capacity of the Kupffer cell to ingest these particles. Actually, it was shown almost ten years ago by Dr. Saba, one of the coauthors, to be due to a depletion of this humoral component.

I would like to add just one additional comment. We have carefully selected patients for study by first assessing them for the prevailing level of opsonic protein. There are some in vitro data available in our laboratory that demonstrate that superheightened levels of opsonic protein may, indeed, be deleterious due to rapid agglutination of particles in vitro in excess of R.E. activity and thus the potential of pulmonary localization. Therefore, we have carefully limited cryoprecipitate infusion to patients with documented hypoopsonemia, and in this setting an effective response is observed.

Reversible Pulmonary Oxygen Toxicity in the Primate

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From the Department of Surgery, Duke University Medical Center, Durham, North Carolina

In order to investigate the effects of high concentrations of oxygen on the lung, experiments were performed on 18 baboons exposed to a humidified environment of 95% oxygen for five days. Open lung biopsies for biochemical assay, histologic and electron microscopic analysis and measurement of tissue respiration were performed before and after oxygen exposure. Pulmonary function was evaluated by measurement of arterial blood gases, compliance, closing capacity (CC), functional residual capacity (FRC), total lung capacity (TLC), residual volume (RV) and vital capacity (VC) before and after exposure and then at seven and 14 days in the animals which recovered. Six baboons removed from the oxygen environment after 96–110 hours and exposed to room air died within three to 20 hours of profound hypoxemia (Pao_2 40 ± 6). The remaining 12 baboons were successfully weaned to room air over a three day period with a return of ABGs to control values (Pao_2 89 ± 2). Electron microscopic analysis of alveolar membranes exposed to 120 hours of hyperoxia demonstrated endothelial cell swelling, interstitial alveolar membrane edema, and an increased predominance of Type II pneumocytes. Lung volume measurements showed significant decreases in TLC (25%), VC (34%), CC/TLC (28%) and dynamic compliance (47%). Biochemical studies indicated a shift toward anaerobic metabolism with a decrease in tissue oxygen consumption, reduced cytochrome oxidase activity, and increased lung lactic acid production. These changes were all found to be reversible in the 12 baboons slowly weaned back to room air.

HIGH CONCENTRATIONS of inspired oxygen are frequently required in the management of respiratory insufficiency in seriously ill surgical patients. Prolonged use of high concentrations of oxygen, however, may result in the development of physiologic and histopathologic changes in the lung which may be fatal. Experimental studies reveal that exposure to oxygen tensions greater than 650 torr for three to five days consistently impairs lung function sufficiently to cause hypoxia and cyanosis upon return to ambient air.[7] Histologic studies of oxygen toxic rheusus monkey lung have shown interstitial edema, perivascular cuffing and increased septal cellularity. Similar pathologic changes have been found in patients following prolonged oxygen therapy.[11] Both primates and humans have demonstrated a decrease in diffusion capacity following prolonged exposure to greater than 95% oxygen, suggesting that impaired diffusion through a thickened alveolar capillary may occur.[5,6]

The present studies were done on baboons in order to evaluate the deleterious effects of oxygen on lung function and the ability of animals to recover following exposure to 95% oxygen for five days.

Methods

Eighteen healthy adult male baboons (Papio cynocephalus) weighing 18–28 kg were quarantined for 45 days prior to study. To be sure all animals were free of disease, chest x-rays, complete blood counts, and skin tests for tuberculosis were performed during the quarantine period. Each baboon was lightly anesthetized with ketamine hydrochloride intramuscularly (10 mg/kg). After initial measurements of rectal temperature and weight, each animal underwent insertion of a tracheostomy tube. Chest x-rays were obtained to verify the absence of significant pulmonary disease following tracheostomy and at various time periods throughout the experiment. A balloon directed Swan-Ganz catheter was inserted via a venous cut-down and positioned in the pulmonary artery under fluoroscopic control and blood samples were obtained for mixed venous lactic acid level. Simultaneous blood samples were obtained from the femoral artery for lactic acid and arterial blood gas determinations while the animal inspired 100% oxygen.

After lung function determinations had been completed and all blood samples obtained, each baboon underwent an open-lung biopsy through a small anterolateral thoracotomy. Tissue obtained underwent biochemical assay, light microscopy, ultrastructure analysis and tissue respiration. After closure of the thoracotomy, repeat arterial blood gas measurements and chest x-rays were obtained to assure recovery of pre-

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•Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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Supported in part by United States Public Health Service Grant HL15877.

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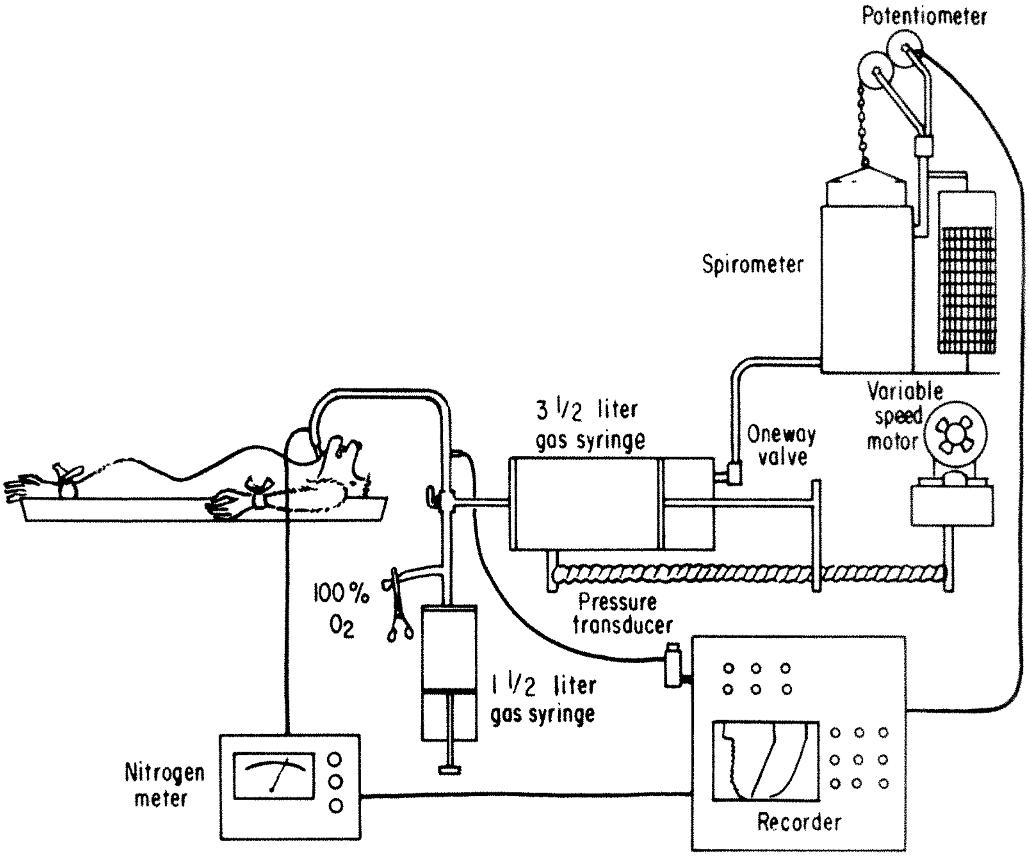

FIG. 1. Diagramatic representation of the apparatus used for measurement of lung volume.

operative function and complete reexpansion of the lung. The tracheostomy tube was then removed and the animals were allowed to awaken in a primate cage in a hyperoxic environment (95% O_2). These studies were then repeated after oxygen exposure and at seven and 14 days following recovery.

All chamber air was passed through a CO_2 absorber and measured P_{CO_2} of the chamber was always less than 10 mm Hg. Relative humidity was measured by a hygrometer within the chamber and remained at 95–100% throughout the exposure. Chamber temperature was stable at 23–25° and chamber pressure remained at one atmosphere at all times. The animals were fed Purina Monkey Chow and water *ad libitum*.

Measurement of Lung Volumes

Measurement of lung volumes in living laboratory animals is difficult at best. To measure lung volume change in the baboon exposed to a toxic level of oxygen, we devised a technique for measuring closing volumes (CV) employing a single-breath oxygen (SBO_2) test modified after that previously described.[8] Closing volume is the lung volume at which small airways begin to close. Measurement of this requires inspiration and expiration between total lung capacity (TLC) and residual volume (RV) at a uniform slow rate. In a paralyzed animal, flow rate decreases exponentially during passive expiration ceasing flow at functional residual capacity (FRC).[2] We have modified the CV measurement using residual gas (nitrogen) technique previously described for testing pulmonary function in conscious humans[3] for anesthetized paralyzed baboons. Closing volumes were measured in a supine position through the tracheostomy with the animal paralyzed and mechanically ventilated with a constant volume animal respirator (Model 607, Harvard Apparatus Company, Millis, Massachusetts). Tidal volumes were set at 10 ml/kg and the rate adjusted to maintain a normal Pa_{CO_2}. The animal's airway was then connected to the apparatus illustrated in Figure 1 to either the 3.5 l gas syringe or the 1.5 l gas syringe via a three-way valve. The 3.5 l syringe was designed so that the cylinder on both sides of the piston was gas-tight. The piston was moved in both directions by a turning screw driven by a variable speed motor (modified from model 607 Ventilator, Harvard Apparatus Company, Millis, Massachusetts). Volume removed from the animal's lung with a 3.5 l syringe was measured by simultaneously determining the volume of gas moving between the cylinder behind the piston and a spirometer (Model P-630 Recording Vitalometer, Warren E. Collins, Inc., Braintree, Mas-

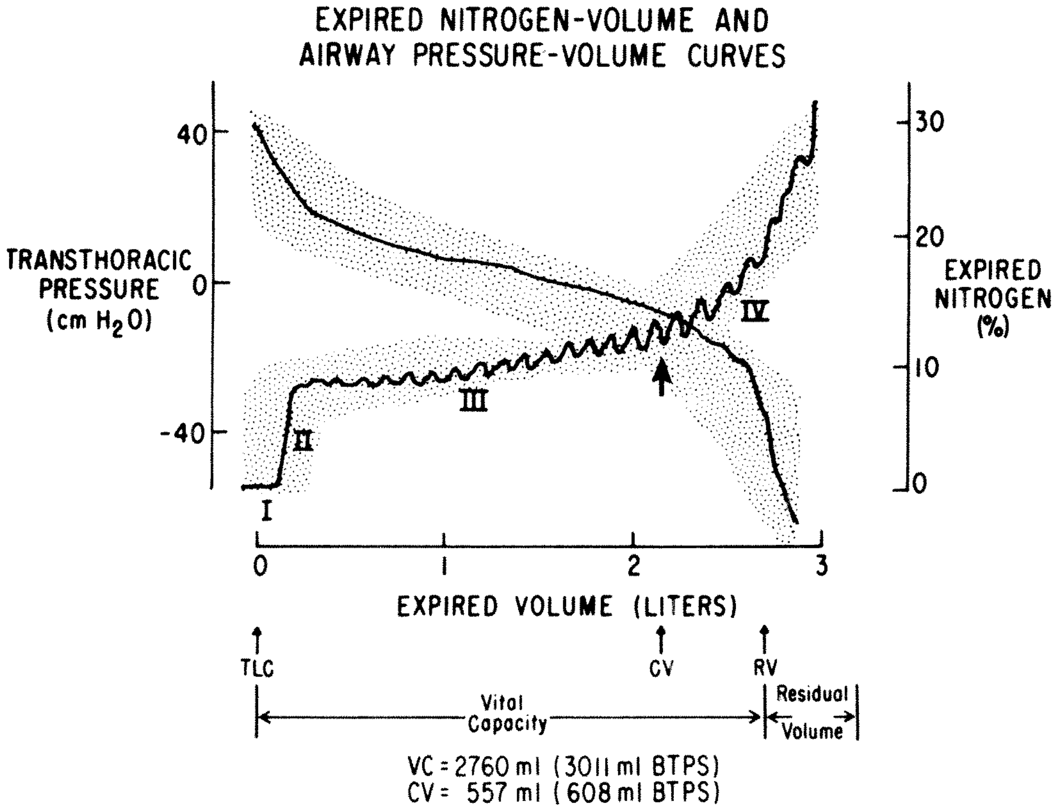

FIG. 2. Reproduction of actual nitrogen and airway pressure curves from which lung volumes are calculated.

sachusetts). Airway pressure was measured using a pressure transducer (Model 1280, Hewlett Packard Waltham, Massachusetts). Expired air at the tracheostomy was analyzed for nitrogen content with the needle midstream in the airway (Nitralyzer, Model 505, Med-Science Electronics). The airway pressure, nitrogen, and expired volume were simultaneously displayed on a multichannel analog recorder (Model 24CRAHA, M.F.E. Corporation, Salem, New Hampshire) (Fig. 1).

After constant ventilation on room air, the apparatus was connected to the animal's tracheostomy tube. Gas was withdrawn slowly from the lungs using a 3.5 l syringe constantly observing the pressure-volume

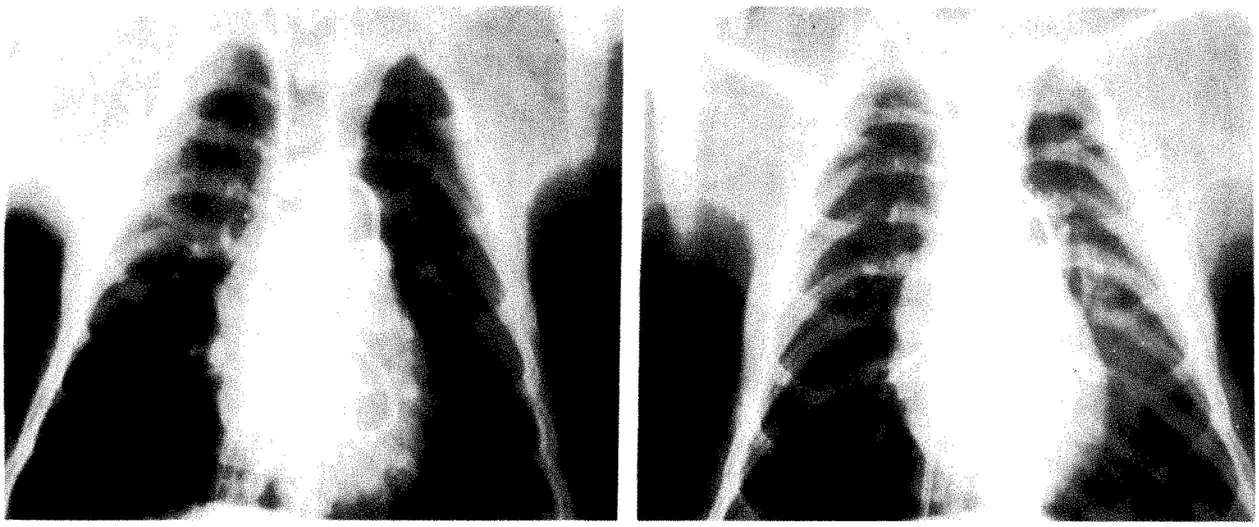

FIG. 3. Chest film before and after exposure to 95% oxygen of the baboon demonstrating absence of any change within the lung fields. The catheters for physiologic measurements are evident within the heart and pulmonary artery.

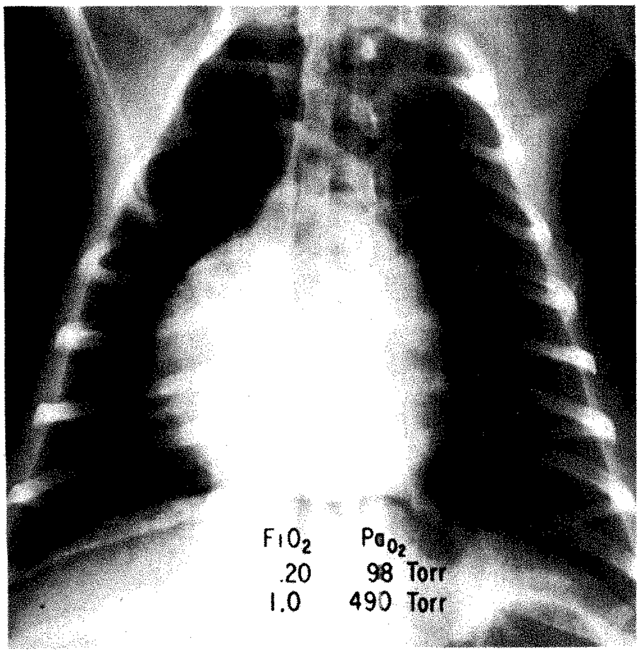

FIG. 4a. Control chest x-ray of baboon; control Pa_{O_2}.

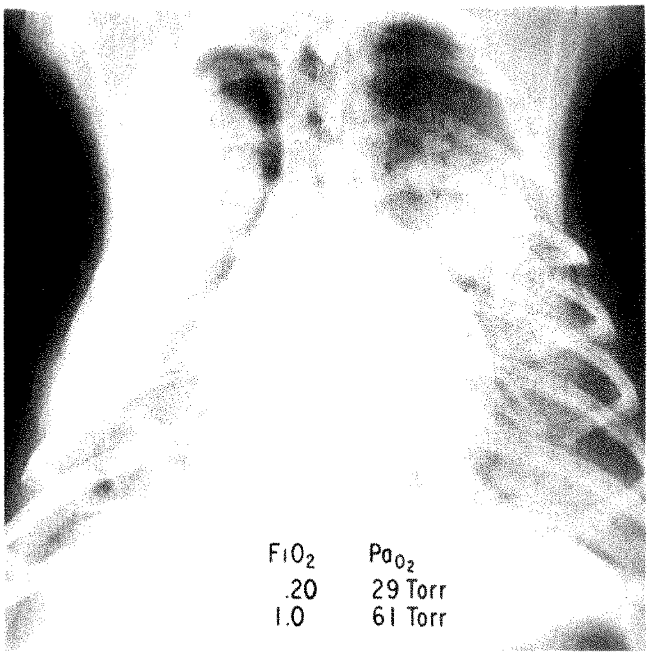

FIG. 4b. Illustration of same baboon with pulmonary edema following exposure to oxygen for 114 hours.

(PV) curve. Volume was removed until the slope of the PV plot became essentially vertical such that a large increase in negative airway pressure resulted in negligible change of volume withdrawn. This point was designated as residual volume and in all cases occurred by a maximum −40 cm H_2O airway pressure. Air was then introduced into the lungs to a point where the PV plot again became vertical; this point was designated total capacity (TLC) and in all cases occurred by a maximum +40 cm H_2O airway pressure.

After the initial pressure-volume curve was established for each animal, the lungs were again deflated to a previously determined RV using the 3.5 l syringe. The three-way valve was then turned and 100% oxygen introduced into the lungs from the 1.5 l syringe until the previously determined TLC was reached. The three-way valve was then immediately turned to its original position and gas aspirated at a flow of 0.15–0.2 l/sec with the 3.5 l syringe until RV was reached. Nitrogen, expired volume, and airway pressure were continuously displayed (Fig. 2). The expiratory flow rate was held constant for any one set of measurements. Between each measurement, the animal was ventilated with room air for at least five minutes. Measurements were repeated until at least three trials of volume introduced into the lungs (inspired vital capacity) equaled or approximated within 5% that volume aspirated from the lungs (expired vital capacity).

Vital capacity in the apneic baboon was defined as the volume between TLC and RV determined from PV measurements.

FRC begins at the point on expiration when the transairway pressure is 0. The volume between this point and RV is designated as expiratory reserve volume; the volume between FRC and TLC is designated inspiratory reserve volume.

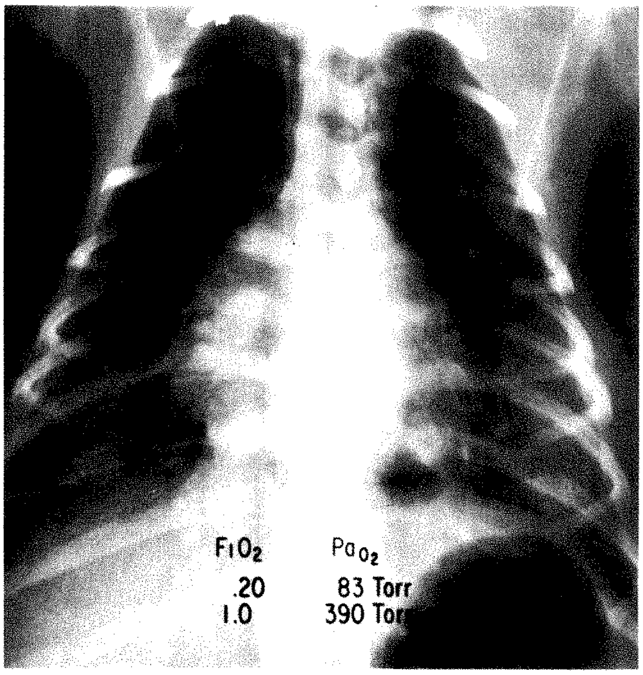

FIG. 4c. Follow-up chest x-ray of the same baboon in the recovery period after weaning back to room air over a period of three days.

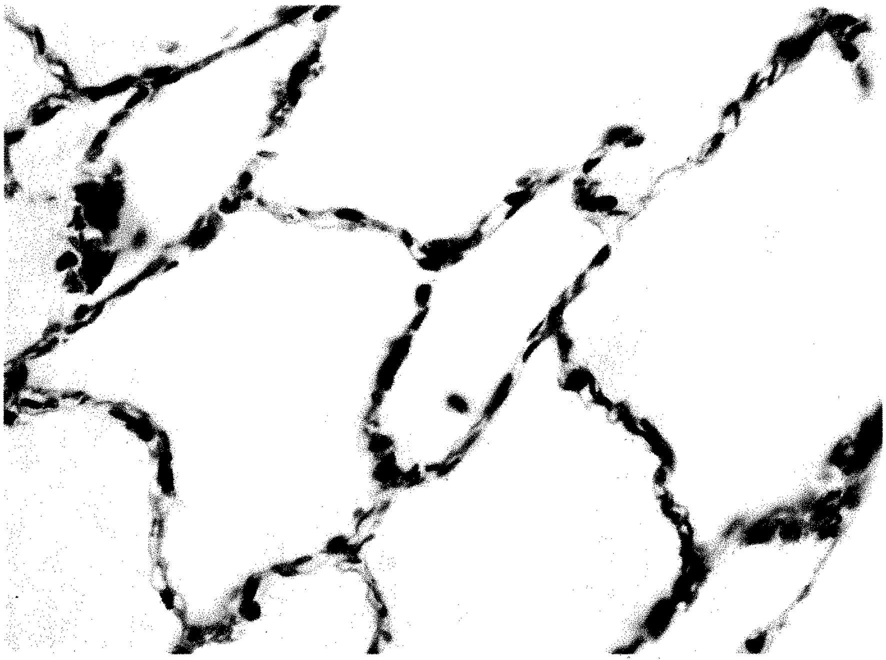

FIG. 5a. Control light microscopic histologic selection of baboon tissue. ×400.

The point on the nitrogen curve where the Phase III slope abruptly increases is the beginning of Phase IV and therefore the point at which airway closure (CV) occurs.[1] The volume between this point and RV is designated as closing volume.

Mean exhaled alveolar nitrogen concentration was measured by the planimetric determination of the area under the nitrogen-volume curve. Ventilatory dead space (V_D) was measured on the respirator by a timed collection of exhaled gas measuring its volume and CO_2 content. Dead space was calculated by using the Enghoff modification of the Bohr equation subtracting out mechanical dead space.

Therefore, after obtaining by direct measurement inspired volume, V_D, expired volume, and mean alveolar nitrogen concentration, the total lung capacity was calculated using the alveolar dilution equation.[4] Residual volume was then derived by subtracting the measured VC from TLC. Thus from a single breath, the following subdivisions of lung volume and ratios were obtained: TLC, VC, RV, FRC, CV, CV/VC, CC, CC/TLC, and RV/TLC.

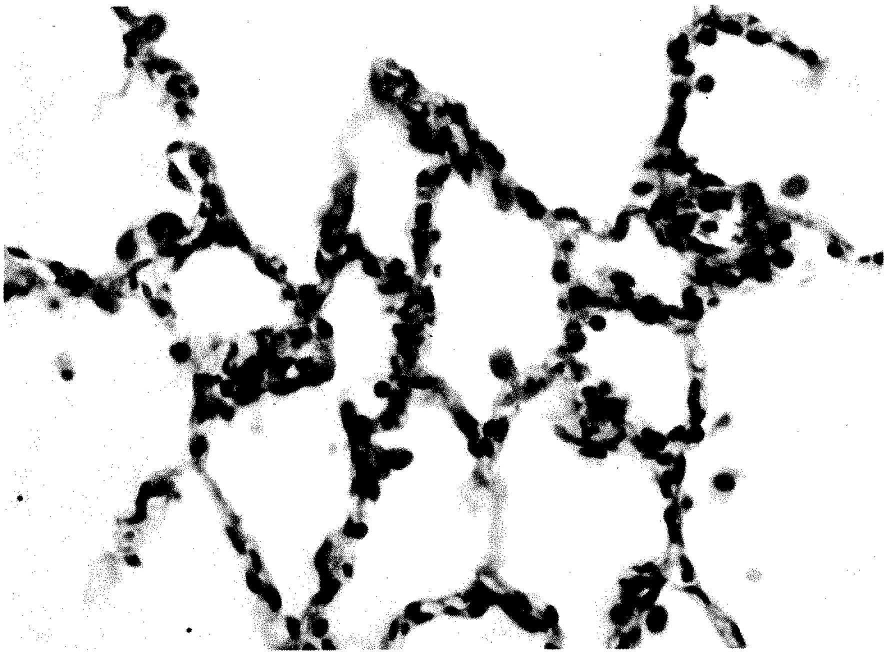

FIG. 5b. The light microscopic appearance of baboon lung after 114 hours of exposure to 95% oxygen. The alveolar capillary septum appears widened and there is evidence of increased cellularity. Hematoxylin and eosin. ×400.

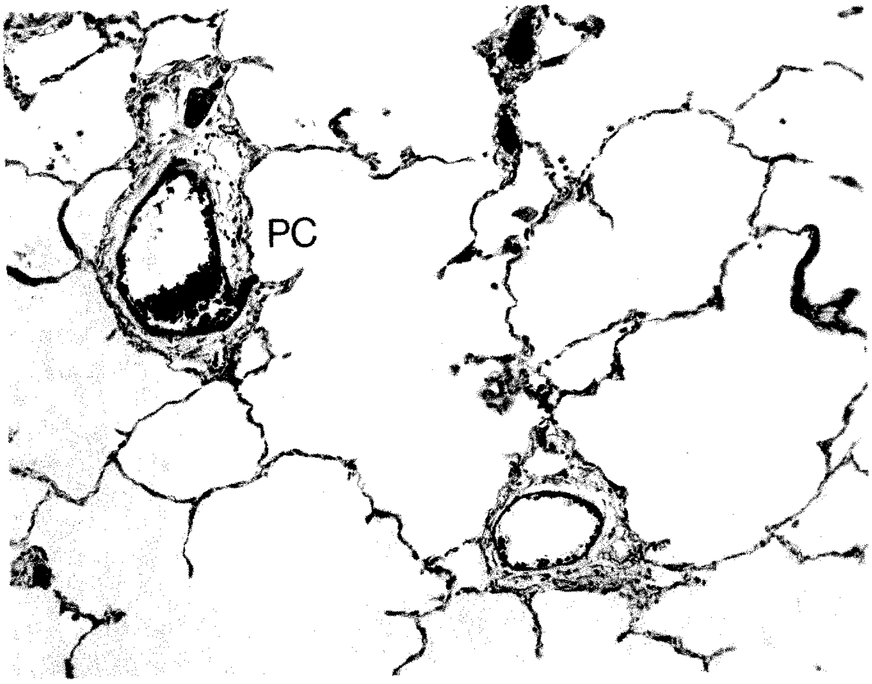

FIG. 5c. Baboon lung after 114 hours of oxygen exposure showing perivascular cuffing (PC). Hematoxylin and eosin. ×250.

Histology and Electron Microscopic Studies

Lung tissue obtained by open biopsy was formalin fixed for histologic analysis and gluteraldehyde fixed for electron microscopic studies by performing the alveolar air spaces at 15 cm H_2O pressure.

Enzymatic Assays

Lung tissue obtained from biopsy specimens weighing approximately 1 g was placed in a tissue homogenizer. Ten milliliters of buffer consisting of 50 mM potassium phosphate, pH 5.7, .1 mM EDTA, and 0.2% Triton X-100 was added to the tissue. After vigorous homogenization, the slurry was filtered through cheesecloth and spun at 10,000 × g for ten minutes. All procedures were performed at 4°. The supernatant was stored in ice until aliquots were removed for measurement of enzymatic activity.[12]

Tissue Respiration

The portion of the biopsy specimen designated for oxygen consumption measurement was immediately weighed wet. Three specimens from each lung biopsy averaging 60–80 mg were individually placed in the tissue chamber of a platinum oxygen electrode system (Rank Brothers, Cambridge, England) and incubated at 37° C in a sterile solution of 1% glucose in 0.9% sodium chloride. Data from the oxygen electrode was displayed on a Heath-Schlumberger Strip Chart Recorder (Model SR 204, Heath Company, Benton Harbor, Michigan). The electrode was calibrated before use and oxygen consumption expressed as nanomoles O_2 consumed per gram of tissue per minute. The value used as the oxygen consumption for each lung biopsy was the mean of measurement from three separate tissue samples from the same biopsy.

Lactic Acid

Serum from blood samples obtained from the femoral pulmonary arteries was assayed for lactic acid concentration by a method monitoring the rate of NAD reduction spectrophotometrically in a system employing the enzyme lactic dehydrogenase.[12] The difference in lactic acid between the two sample sites (femoral artery-pulmonary artery) reflects the amount of lactic acid added to the circulation by the lungs.

The significance of the differences in data obtained from the control, oxygen toxic, and recovery periods were assessed using the paired Student's t-test. A p value of <0.05 was considered statistically significant.

Results

Animal Survival

During the first 48 hours, the animals ate and drank normally and were active. However, they became less active and anorectic by 72 hours. Two animals were removed at 96 hours because they appeared ill, dyspneic, and cyanotic. They underwent an entire set of studies and lung biopsy and were returned to 95% oxygen environment for slow return to room air levels over three days. These two animals died. However, the

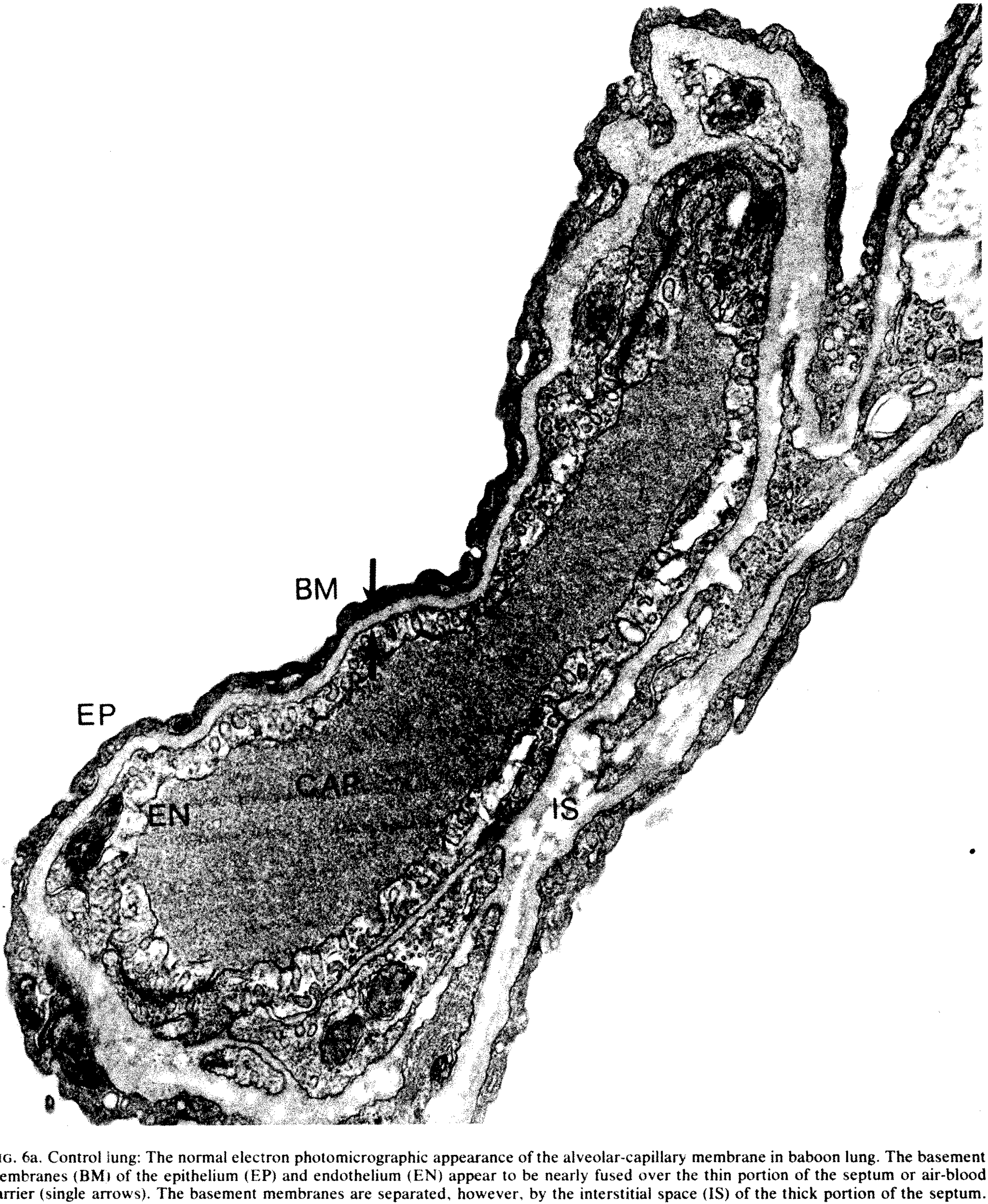

FIG. 6a. Control lung: The normal electron photomicrographic appearance of the alveolar-capillary membrane in baboon lung. The basement membranes (BM) of the epithelium (EP) and endothelium (EN) appear to be nearly fused over the thin portion of the septum or air-blood barrier (single arrows). The basement membranes are separated, however, by the interstitial space (IS) of the thick portion of the septum. The capillary lumen (CAP) is widely patent. (This and subsequent tissues were fixed by perfusion of the air space with 4% glutaraldehyde and later stained with uranyl acetate; original magnification ×6,700).

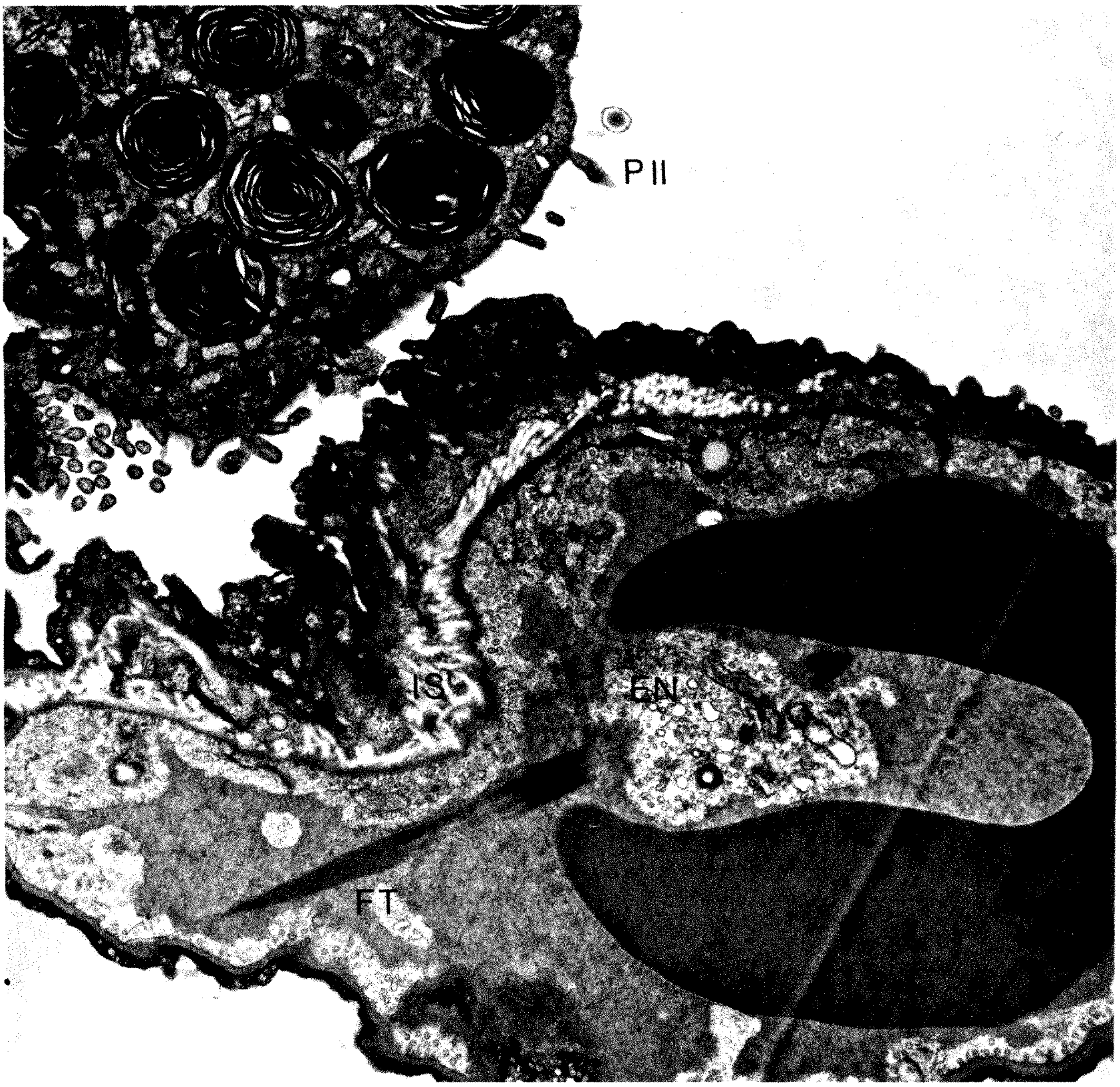

FIG. 6b. Lung after exposure to 95% oxygen for 114 hours. Type II pneumocytes (PII) containing multiple osmophilic lamellated inclusion bodies appeared more predominantly than in control lung. The endothelial cells (EN) were markedly swollen and often encroached upon the capillary lumen. The interstitial space (IS) was widened. Rarely could fibrin tactoids (FT) be identified. The basement membranes of both the endothelial cells and epithelial cells remained intact; original magnification ×12,000.

other animals completed the entire protocol including recovery stages. Six baboons abruptly returned to room air 96–110 hours uniformly died, usually within three to 20 hours, of profound hypoxemia with a mean Pa_{O_2} 40 ± 6 mm Hg.

Radiographic Changes

The chest x-ray in most of the animals studied did not demonstrate any active change in the lung fields (Fig. 3). However, two animals did exhibit obvious pulmonary edema after 120 hours of hyperoxia. One of these was successfully weaned from oxygen and the chest film subsequently returned to normal as did the arterial blood gas measurements (Figs. 4a–c).

Morphology

After oxygen exposure, histologic analysis revealed increased alveolar cellularity and occasional areas of

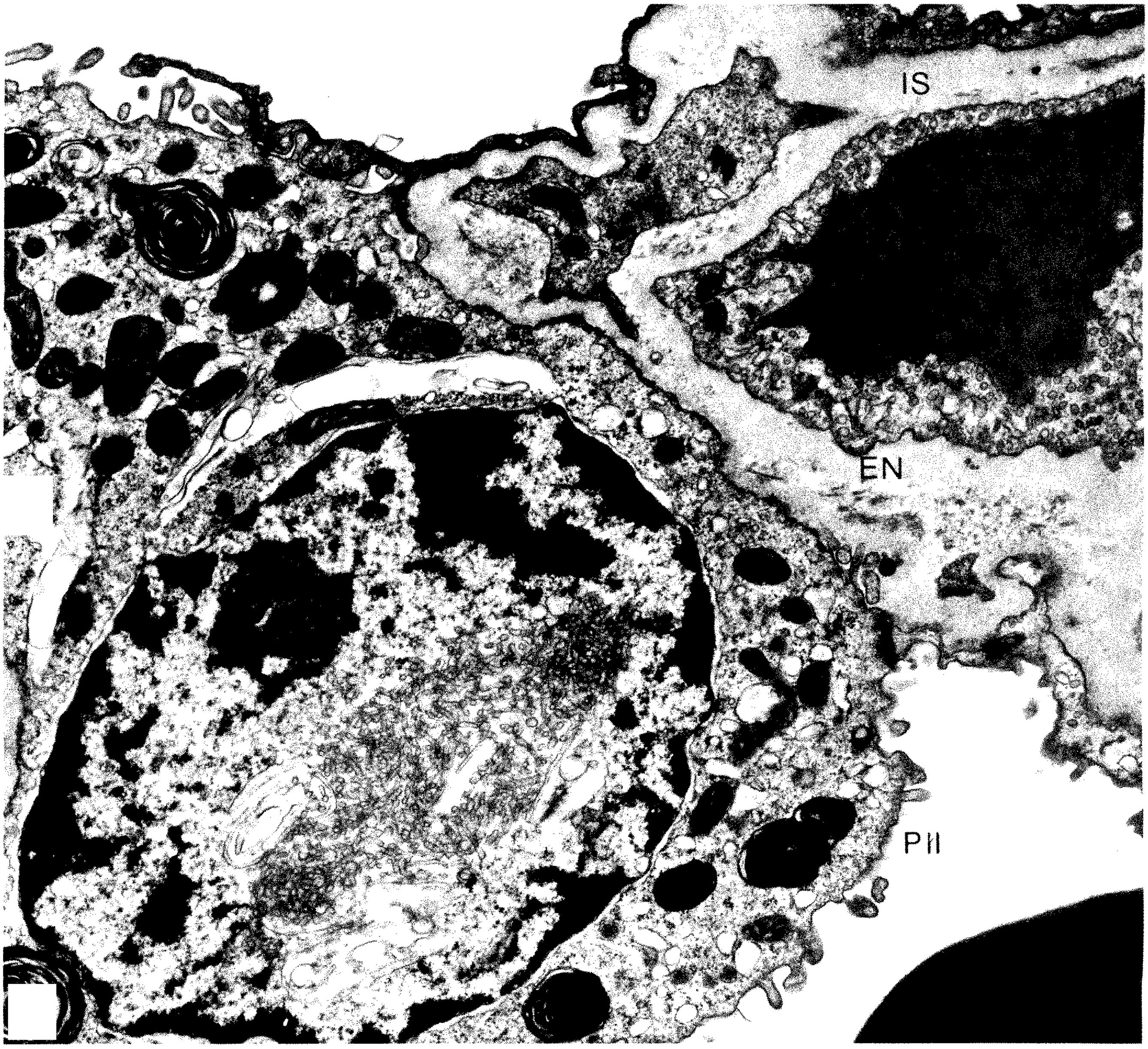

FIG. 6c. Lung after exposure to 114 hours at 95% oxygen. A large Type II pneumocyte is shown (PII). The interstitial space (IS) at the alveolar capillary membrane is widened and endothelial cells (EN) are swollen: original magnification ×6,700.

perivascular edema compared to control biopsy (Figs. 5a–c). Electron microscopic analysis following hyperoxia consistently revealed endothelial cell swelling, edema of the interstitial alveolar membrane, and an increased predominance of Type II alveolar cells with osmophilic lamellated bodies frequently seen extruding into the alveolar air spaces. All of these findings are pathognomonic of the oxygen toxic lung. Only rarely were signs of alveolar membrane disruption or intravascular coagulation observed (Figs. 6a–e). Morphologically the lesion characteristic of acute oxygen toxicity was no longer present after seven to ten days of recovery.

Arterial Blood Gases

After exposure of these animals to 95% oxygen there was a sharp drop in Pa_{O_2} from a normal mean value of 89.0 ± 2.0 mmHg to a mean of 50 ± 4 mmHg Pa_{O_2} in the oxygen toxic animal breathing room air ($p < 0.005$). Removal of the baboon from the oxygenated environment and re-exposure to room air resulted in profound

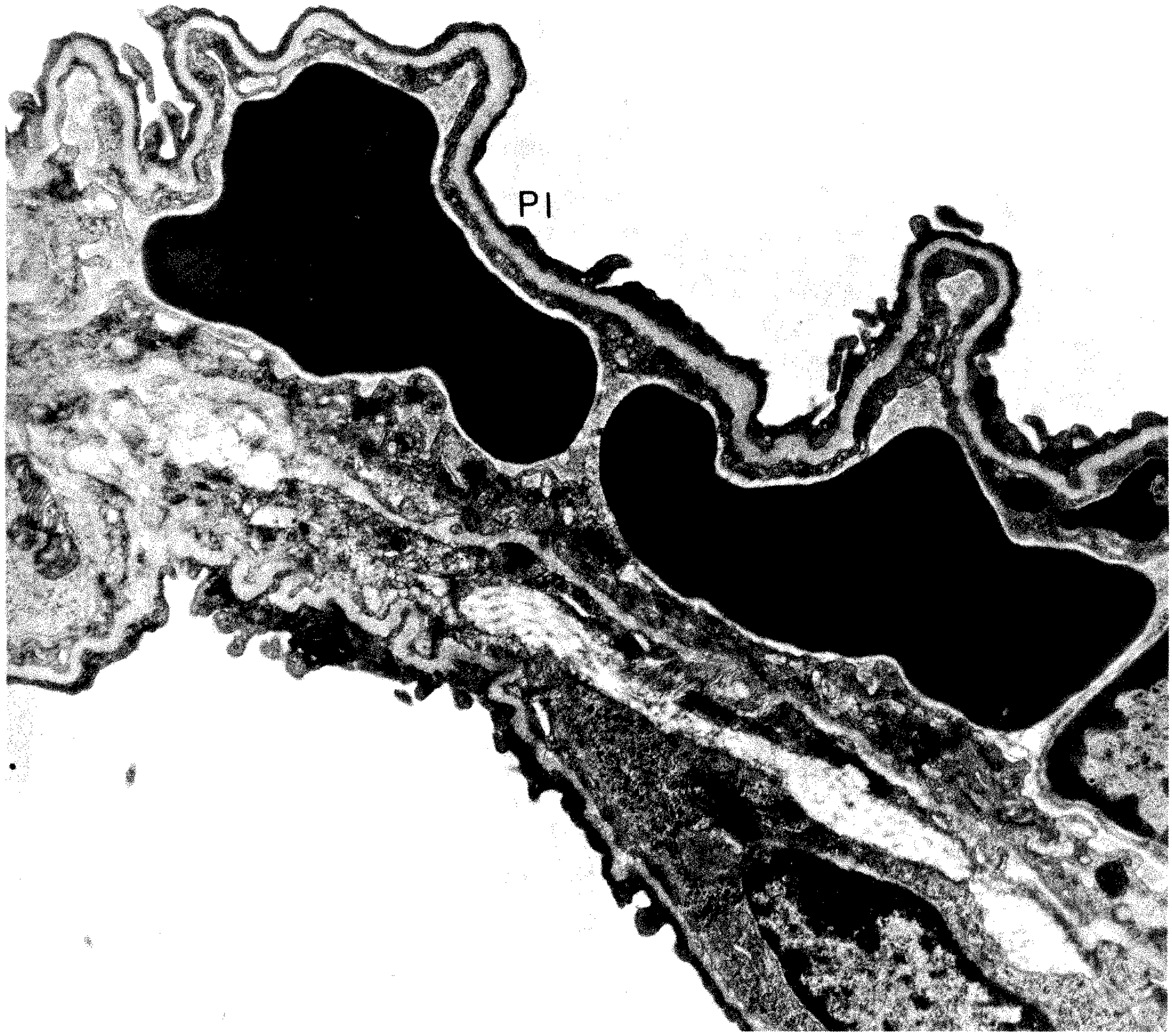

FIG. 6d. Lung after two week recovery period following 114 hours 95% oxygen exposure. Type I pneumocytes predominate (PI). The interstitial space is no longer edematous. Endothelial cells (EN) although slightly swollen no longer encroach upon the capillary lumen. Basement membranes (BM) of both the alveolar epithelium and endothelium are intact. (×6,700)

hypoxemia leading to death if supplemental oxygen was not provided. However, if the baboon was gradually weaned back to room air, the blood gases were found to return to pre-exposure values, Pa_{O_2} 88 ± 5.6 vs control Pa_{O_2} 88.8 ± 1.7. Although there was variability in the degree of impairment in oxygenation, the decrease was consistent and significant, an average decrease of 44% from control levels. However, after

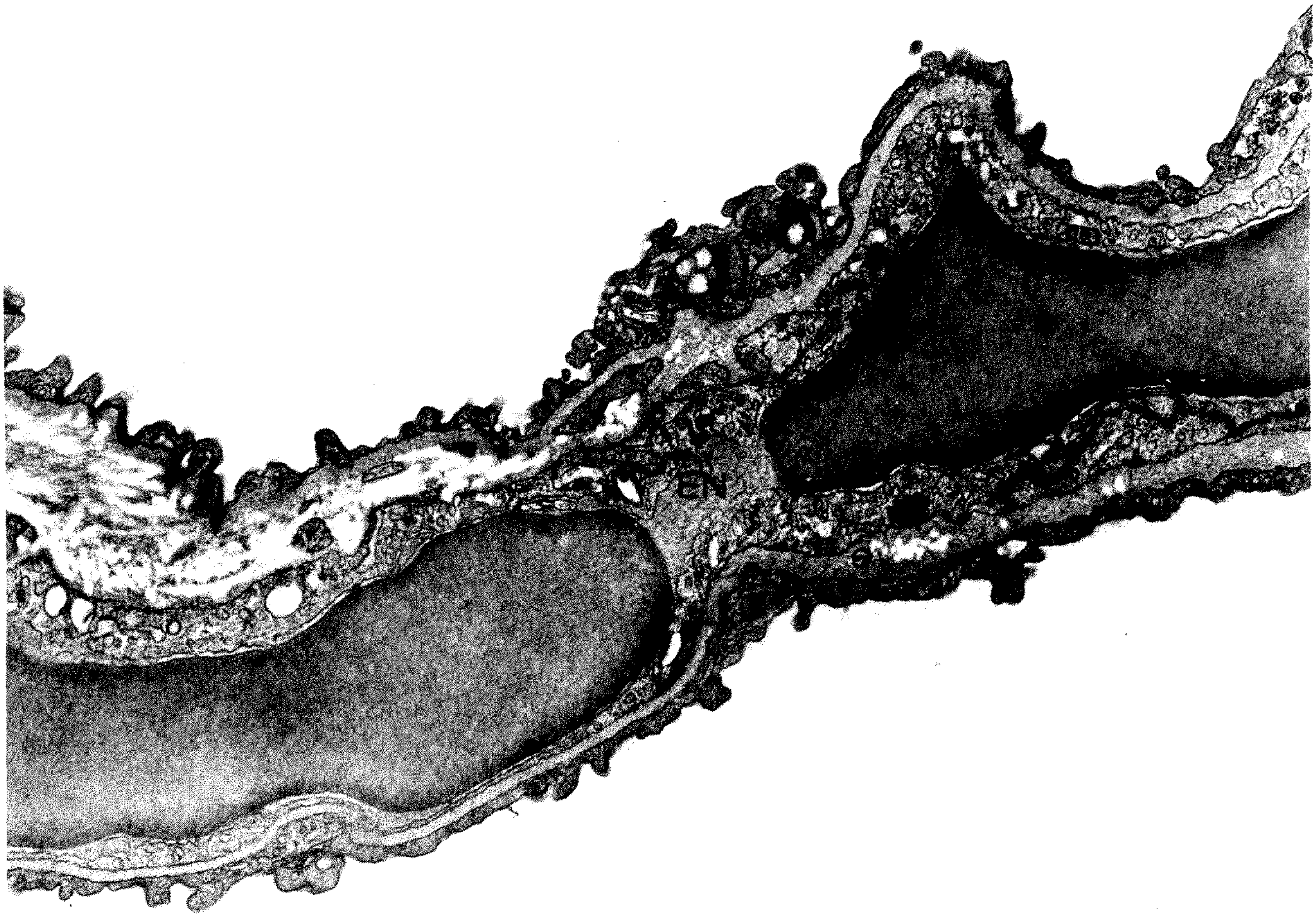

FIG. 6e. Lung after two weeks of recovery. Slight endothelial cell swelling persists (EN) but the lung otherwise has the appearance of control lung (Fig. 1); original magnification ×6,700.

recovery Pa_{O_2} returned to 88.0 ± 5.6 mmHg, a value not significantly different from pre-exposure values (Fig. 7).

Lung Volumes

Lung function measurements demonstrated a significant decrease in total lung capacity, vital capacity, and dynamic compliance, with a significant increase in residual volume (Figs. 8 and 9).

Enzymes

Enzyme activity was measured for superoxide dismutase (SOD), catalase, glucose-6-phosphate dehydrogenase, and cytochrome oxidase. SOD revealed a significant decrease after exposure to 95% O_2 for 120 hours. The mean decrease was to 68% of control activity ($p < 0.005$) immediately after oxygen exposure but rose to a level not significantly different from control after two weeks of recovery. Catalase activity showed no significant change while glucose-6-phosphate dehydrogenase rose to 172% of control activity in the toxic animal. Recovery values were variable but not significantly different. Cytochrome oxidase demonstrated significant decrease in activity to a mean 64% of control, whereas after two weeks of recovery it was not significantly different from the control.

Tissue Respiration

Oxygen consumption by lung tissue in six animals was observed to decrease from a mean of 48.8 ± 1.9 nmoles of O_2 consumed/g tissue/minute in the control to 30.5 ± 4.9 nmoles O_2/g tissue/minute in the oxygen toxic animal representing a 37.5% decrease, with a p value < 0.005. After recovery, the values increased to a level not significantly different from control.

Lactic Acid

In five animals, lactic acid produced by the lung increased significantly from the mean control value of 0.5 ± 0.2 mg/dl to an oxygen toxic value of 3.06 ± 0.7 mg/dl ($p < .05$) a 612% increase (Fig. 10). Following recovery after oxygen exposure, the lung lactic acid production returned to the control level. It was also noted that the absolute arterial serum lactic acid level rose from control mean 11.9 ± 1.3 mg/dl to an oxygen toxic value of 31.3 ± 6 and then returned to 13.8 ± .7 mg/dl with recovery.

Discussion

It is ironic that all aerobic organisms require oxygen to live, yet, high concentrations produce deleterious effects leading to death from hypoxemia. In mammals, the primary damage at atmospheric pressure occurs in the lungs and the signs are those of progressive respiratory failure. Although the degree of oxygen exposure necessary to cause deleterious effects varies among species and among individual members of the same species, all nevertheless will eventually succumb to its toxicity.

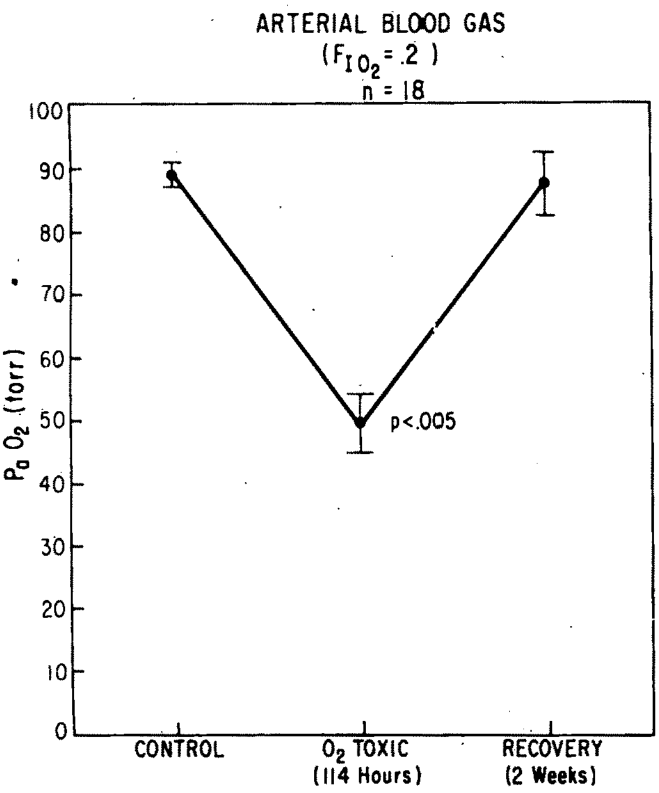

FIG. 7. Change in arterial blood gas from control at completion of exposure to 95% oxygen and then at recovery at two weeks (after the animal has been removed from the oxygen and returned to room air).

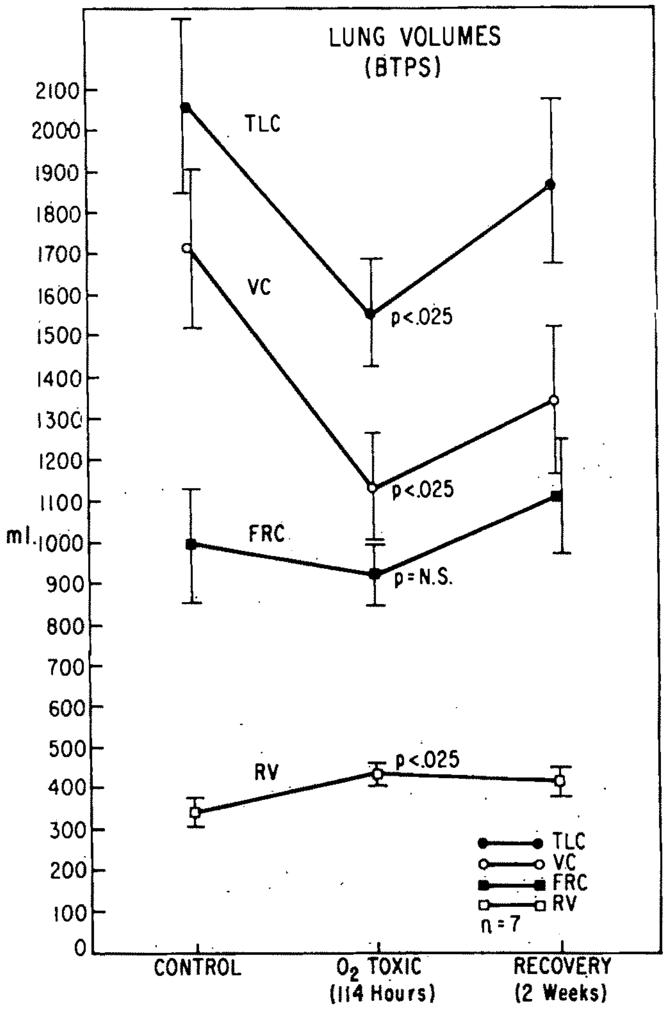

FIG. 8. Illustrates the changes in lung volumes following exposure to oxygen and at recovery. Significant changes are indicated.

These studies demonstrate a reproducible lesion in the baboon lung exposed to hyperoxia. The electron microscopic changes described are characteristic of oxygen toxicity. Although the lesion is subtle by light microscopic examination, it is our feeling that the changes observed are real and attributable to oxygen toxicity. The electron microscopy changes of the endothelial cell swelling, interstitial alveolar membrane edema, and increased predominance of type II pneumocytes parallel closely with the observation made previously in oxygen toxic primate lungs.[6,9]

One of the major studies in man evaluated four volunteers who breathed 98% oxygen for 30, 48, 60, and 74 hours respectively.[5] In these volunteers there was a fall in vital capacity that progressed rapidly. Also, the chest x-ray revealed no abnormalities and the

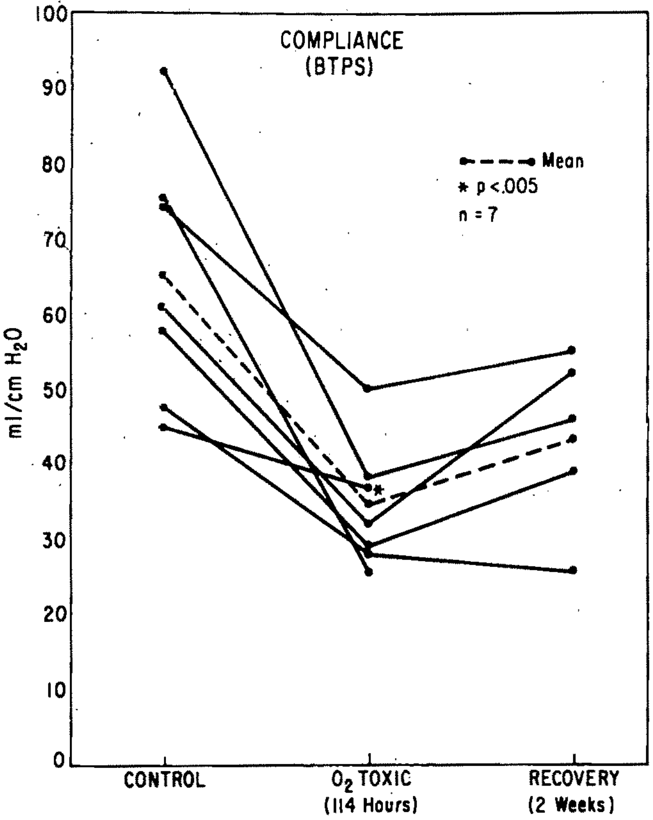

FIG. 9. This graph demonstrates the change in compliance following exposure to 95% oxygen. The significant change in mean values is indicated by the p value of <.005.

physical examination was within normal limits. In the majority of the animals used in our studies, the chest x-rays have been normal. Lung function studies demonstrated a decrease in lung volumes, specifically a decrease in vital capacity which parallel these initial studies in man. Similar to the studies of Caldwell,[4] lung volumes returned to normal once baboons were removed from oxygen. The recovery period, however, was variable and one animal required several weeks before his vital capacity returned to control value.

The reason for the decrease in vital capacity remains unclear. However, in our morphologic studies as in the previously mentioned human studies the decrease in vital capacity may be related to the fluid accumulation in the interstitial space. This could account not only for the fall in vital capacity but also the decrease compliance and the diffusion capacity seen in man.

Also of interest is the apparent increase in anaerobic metabolism in the lung in an animal exposed to high concentrations of oxygen. The end product of anaerobic metabolism of glucose is lactic acid. Therefore increase in lung lactic acid may be assumed to be an accurate measure of anaerobic metabolism occurring within the lung. We found a striking increase of 612% in lung lactic acid production in these animals breathing 95% oxygen. This was far greater than the increase in lactic acid noted in the serum. Previous studies have shown no significant change in cardiac output in the baboon following exposure to oxygen[10] which we feel negates the possibility that decreased tissue perfusion might account for the increased lactic acid. Even a decrease in Pa_{O_2} after exposure to 95% oxygen should not cause significant tissue hypoxia to account for this dramatic rise in lactic acid. Simon, Robin and others[13] have demonstrated that Type II cells undergo active anaerobic metabolism. Perhaps the most logical explanation is that the proliferation of these cells in the lung following injury secondary to oxygen exposure is the cause of the increase in lung lactic acid production. The stimulation of Type II cells is seen in many conditions of lung injury. It may well be that lung lactic acid would be a sensitive indicator of extended lung injury and its fall an indication of recovery from that injury.

It appears that the exposure of primate lung to 95% oxygen can produce a distinct morphologic, physiologic and biochemical change which markedly impairs the lung function and will produce progressive hypoxemia. It must be remembered that pure oxygen toxicity itself

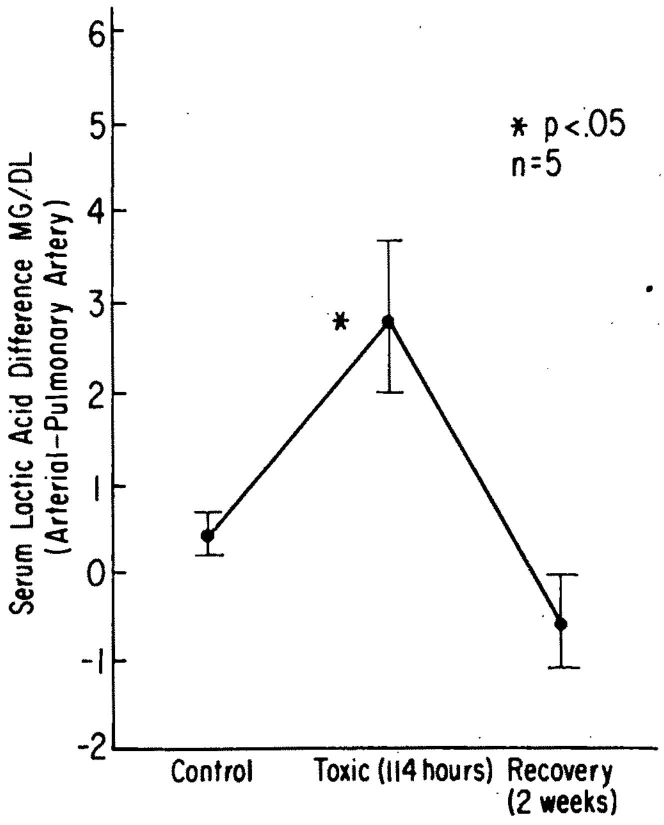

FIG. 10. Illustrates the increase in lung lactic acid production after exposure to 95% oxygen.

produces minimal if any radiographic changes. Physiologically, there is progressive hypoxemia and decrease in lung volumes with an increase in lung water. Biochemical changes indicate an increase in anaerobic metabolism within the lungs characterized by decreased tissue, superoxide dismutase, decreased tissue oxygen consumption, increased lactic acid production, increased lung G-6-PD activity and decrease in cytochrome oxidase activity. An important feature in its clinical applications is that the abrupt withdrawal of oxygen after prolonged exposure clearly leads to severe hypoxemia and death. However, if careful attention is paid to lung volumes and to ventilation and the oxygen concentration is gradually reduced, the pulmonary lesions are clearly reversible and survival may well be anticipated.

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DISCUSSION

DR. CHARLES K. MCSHERRY (New York, New York): I commend the authors for performing the experiments on the nonhuman primate. Our experience suggests that the data obtained from studies in the nonhuman primate are more relevant to the human situation than studies carried out in other animal species.

The electron photomicrographs show an increase in the number of inclusion bodies in the cell. The appearance suggests that perhaps these are an increase in the Golgi apparatus. Work in our laboratory by Dr. Helena Gilder suggests that oxygen not only inhibits the synthesis of surfactant but also its intracellular transport—the latter manifested by an increase in the Golgi apparatus.

I would like to know if the essayist has any data on surfactant production or synthesis in these animals.

DR. WALTER G. WOLFE (Closing discussion): Yes and no on surfactant. We have not looked at it in the primate. We did some work in the dog, using ^{32}P uptake as a way to indicate whether there is an increase or a decrease in surfactant, or whether it was being exhausted, over time causing absorption atelectasis—we find surfactant to be unchanged. In the baboon I have not looked at whether there is an increase or decrease in actual surfactant quantitatively in the baboon lung.

The Dynamics of Utilization Review: A Case Study of 44 Massachusetts Hospitals

PAUL M. GERTMAN, M.D.,* RICHARD E. EGDAHL, M.D.†

Utilization review programs have existed on a national basis for over a decade, but relatively little is known about the patients who are scrutinized and what actions are taken to correct unnecessary use. In the fall of 1976, 44 of the 122 Massachusetts hospitals participated in a two-week in depth study of their utilization review activities. Over 22,000 admission and extended stay reviews were performed during this time period, and of these, 2,120 patients' continued stays in the hospital were questioned. In five admission review cases and 79 extended stay review cases, the UR committee formally terminated continued health insurance benefits, and in 12 admission reviews and 74 extended stay reviews, questioning by the UR committee led the attending physician to discharge the patient earlier than would have otherwise occurred. Ninety-four percent of the terminations occurred in Medicare patients and the median age of these patients exceeded 80 years. For medical patients, a disproportionate share of all those cases questioned and of those terminated occurred in chronic illness categories, such as cancer, heart failure, and organic brain syndromes. A higher than expected percentage of surgical cases questioned by the UR committee were in neurosurgical, cardiovascular and orthopedic procedure groups. The frequency with which UR committees identified and acted upon cases suggests that effective self-policing is occurring. A large portion of the utilization problem, however, may be related to the unavailability of appropriate sub-acute care for patients with chronic medical illness or surgical procedures which require long postoperative rehabilitation and recuperation.

From the Boston University School of Medicine, Boston, Massachusetts

IN THE UNITED STATES, well over a million hours of physician time is spent each year on hospital utilization review activities and probably tens of thousands of additional hours are spent on related activities at the PSRO and Medical Society level.[1] Yet, little is really known about the types of UR activities being carried out, how they are performed at the hospital level, who they affect, and what the results of such programs are. Our Health Care Research group at Boston University has undertaken a series of studies over the last several years in an attempt to better delineate the nature of utilization review (UR) activities and their impact.

One of these studies is reported here; it was an in depth, two-week prospective case study of the utilization review process in 44 Massachusetts hospitals. In this study every patient whose stay was reviewed and questioned in any way by the UR process was tracked with respect to: a) the patient's characteristics, b) the activities of the UR coordinator and the UR physicians in the case, and c) the resultant actions that took place. In order to identify possible systematic patterns, these result measures were then examined in relation to the characteristics of the individual patients, the characteristics of the hospitals, and the characteristics of the UR programs.

Methods

The study was designed and analyzed by Boston University staff in conjunction with the Massachusetts Utilization Review Association (MURA), a statewide organization representing UR coordinators in about 65 hospitals. All hospital administrators and UR coordinators in Massachusetts were contacted about their willingness to participate. The cooperation of 44 of the 122 hospitals and their UR staff was obtained. As shown in Table 1, although larger hospitals were slightly overrepresented, the participants came from a good cross-section of small and large, private and religious and teaching and nonteaching Massachusetts hospitals.

Hospitals in the study were asked to log the number of admission and extended stay reviews done every day for a two-week period. They then identified the cases they were not able to approve upon their initial examination of the record—i.e., cases whose certification of necessity for continued hospital stay was *questioned* for any reason.

In each of these questioned cases, the coordinator filled out a multipart form; one component asked for the patient's medical and demographic characteristics. The second component required a detailed description of the UR decision-flow process from the point of

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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questioning until either the final UR decision was made or the patient was discharged. The following kinds of information was to be included in this section: descriptions of contacts made with the attending physician and by whom they were made, the number of UR physicians who questioned the case, the dates for each step, etc. In cases where the patient was discharged before the UR system had been employed to approve the patient's continued stay or recommend termination of insurance coverage, the coordinator was asked her opinion on whether the patient had voluntarily been discharged earlier than he would have been without the scrutiny of the UR program. Such cases were termed "voluntary early discharges" or "VEDs".

The senior UR coordinator at each hospital was additionally requested to complete a short questionnaire on basic hospital characteristics including: number of beds, type of ownership and training programs, UR program coverage (different third-party beneficiaries reviewed, performance of admission and/or extended stay review for each payor group and sample vs. total review of a payor group) and the policies regarding contact with the attending physician. Coordinators were asked specifically whether they could make any continued stay approvals, whether they were allowed to contact the attending physician on their own initiative and whether they could discuss the appropriateness of the patient's stay with him or only obtain objective information. The questionnaire also asked whether the UR physician reviewing a case ever attempted to remain anonymous with respect to the attending physician. It was felt that these contact policies might affect the dynamics of the review process. The first round of hospitals started their two-week study periods in August 1976 and the last hospital completed its data collection by the end of October 1976.

TABLE 1. *Respondent Hospital Characteristics*

	Number of Respondents	Number of Massachusetts Hospitals* Per Category
Bed Size		
0– 99	6 (13.6%)	30 (20.0%)
100–199	11 (25.0%)	37 (29.7%)
200–299	14 (31.8%)	27 (51.9%)
300–399	8 (18.2%)	16 (50.0%)
400+	5 (11.4%)	12 (41.7%)
Ownership Status		
Non-profit, voluntary religious	6 (13.6%)	103 (35.0%)
Non-profit, voluntary non-sectarian	30 (68.2%)	
Non-profit, public city	6 (13.6%)	12 (50.0%)
For-profit, single	1 (2.3%)	7 (14.3%)
No response	1 (2.3%)	
Teaching Status		
Major medical school affiliation	8 (18.2%)	34 (61.8%)
Limited medical school affiliation	13 (29.5%)	
Independent internship/ residency training program	3 (6.8%)	4 (75.0%)
No physician training program	16 (36.4%)	79 (20.3%)
No response	4 (9.1%)	

* Data on five hospitals' teaching status not available.

Results

Characteristics of Hospital UR Programs: In Massachusetts, as elsewhere in the country, hospital UR programs were in a tremendous state of flux during the latter part of 1976. There was confusion about the exact nature of Medicare and Medicaid requirements; Massachusetts had a state Medicaid review program which was being phased into the PSRO program, local PSRO's were at various stages of development in Massachusetts, and private insurance companies were allowing but not requiring hospitals to perform concurrent utilization review. Categorizing review programs by the number of major payor groups reviewed,* whether an admission and/or extended stay review was done for each payor, and whether all patients or only a sample were reviewed in each payor group, nine different basic patterns were identified in this sample of hospitals.

This diversity of hospital concurrent UR programs in participating hospitals appeared even greater when we asked about basic policies regarding the role of the UR coordinator and the physician in performing concurrent review. As shown in Fig. 1, only slightly more than 50% of hospitals allowed the UR coordinators to certify stays, to contact the patient's attending physician on their own initiative, and to discuss with the attending physician the appropriateness of a patient's continued hospitalization. Another important policy of hospital UR programs was the extent to which UR physician advisors or committee members interacted with an attending physician when a case was questioned. When asked, "How often do reviewing physicians attempt to remain anonymous?", the responses were as follows: never, 72.7%; rarely, 13.6%; occasionally, 6.8%; almost always, 4.5%; and always, 2.4%. As might be expected, the greater the frequency of physician anonymity in dealing with the attending physician, the greater the UR coordinator's discretionary authority (Kendall correlation coefficient = 0.294, $p < 0.03$). If one simply dichotomizes the hospital's UR coordinator's authority into restricted vs. unrestricted and the UR physician anonymity into never vs. ever, and then cross tabulates this by the nine different types of review coverage, 25 different descriptive categories of hospital review programs were identified among our 44 participating study

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* The major payor groups were defined as Medicare, Medicaid, Blue Cross, commercial insurance and self-pay.

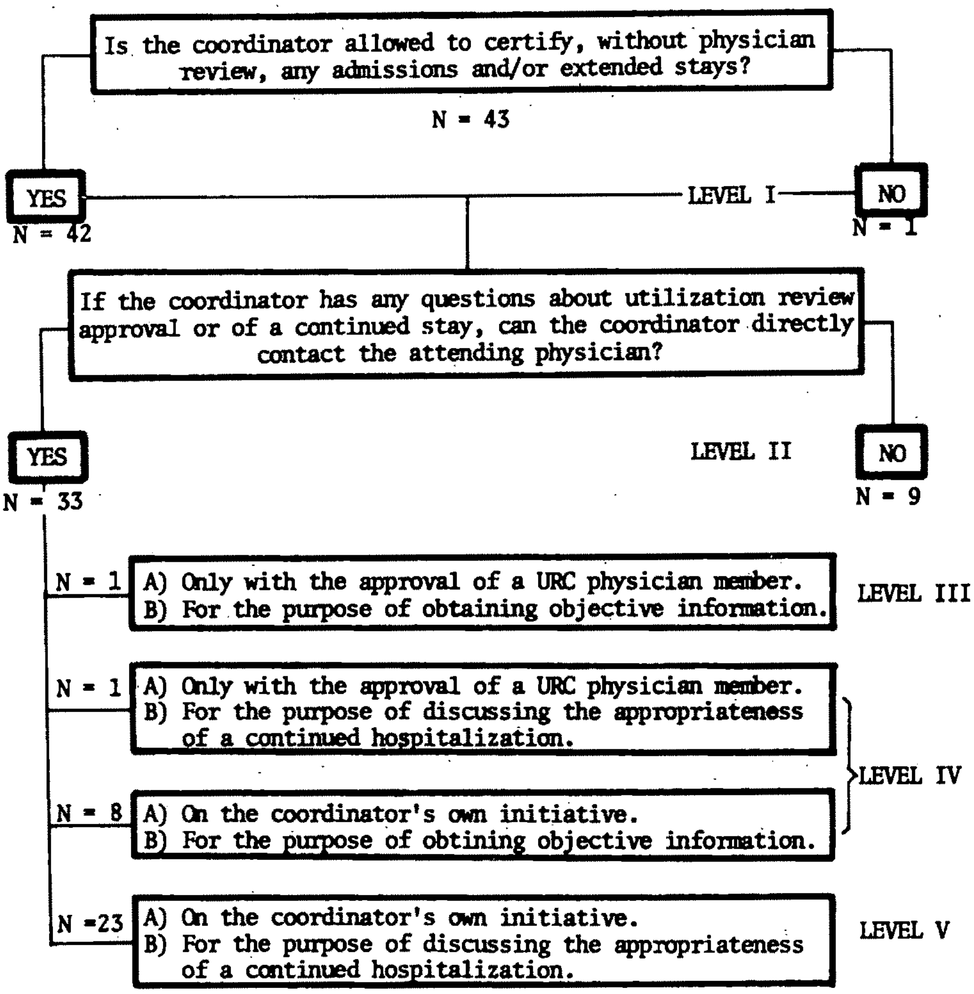
Is the coordinator allowed to certify, without physician review, any admissions and/or extended stays?
N = 43
YES
N = 42
LEVEL I
NO
N = 1
If the coordinator has any questions about utilization review approval or of a continued stay, can the coordinator directly contact the attending physician?
YES
N = 33
LEVEL II
NO
N = 9
N = 1
A) Only with the approval of a URC physician member.
B) For the purpose of obtaining objective information.
LEVEL III
N = 1
A) Only with the approval of a URC physician member.
B) For the purpose of discussing the appropriateness of a continued hospitalization.
LEVEL IV
N = 8
A) On the coordinator's own initiative.
B) For the purpose of obtining objective information.
N =23
A) On the coordinator's own initiative.
B) For the purpose of discussing the appropriateness of a continued hospitalization.
LEVEL V

FIG. 1. Differential patterns of UR Coordinator authority in case study hospitals.

hospitals, with 17 of these being unique to a single hospital.

UR Actions in Study Hospitals

In the two-week study period, over 22,000 admission and extended stay reviews were performed in the participating hospitals which supplied complete review volume information. As shown in Table 2, 2,120 (10%) of these reviews led to the patient's continued stay being questioned. Follow-up data was missing for 18 cases, 1,842 were eventually approved for continued stay, 84 had their health insurance benefits terminated, and 176 were discharged prior to a final UR action. In this latter group, 58 were definite voluntary early discharged, 55 were definitely *not* voluntary early discharges, and some data was missing for 63; in the latter group, 28 patients were classified as possible VEDs based on the fact that the attending physician was contacted by the UR staff and the patient was discharged within 24 hours. Thus, of the questioned cases, ultimately 170 patients had their benefits terminated or represented a voluntary early discharge. There were several important contrasts between the two types of review. Over 17% of extended stay reviews were questioned as compared to less than 1% of admission reviews. Of those cases questioned, however, 18% of the admission cases resulted in early discharge or termination compared to less than 8% of the extended stay cases.

As shown in Table 3, 24 hospitals had one or more terminations in the two-week study period, 22 had a definite voluntary early discharge and 34 of the 44 (77%) had either a termination or a definite voluntary early discharge; inclusion of the possible VEDs does not change this latter figure. Events such as terminations of VEDs in a two-week period in a particular hospital may be relatively uncommon, yet not absent in every two-week period. A study of review results over a one-year period might find almost all hospitals having had at least one case where UR had a direct limiting effect on a patient's continued stay in the hospital.

TABLE 2. *Summary of Utilization Review Activity*

Reviews Performed	No. Reviews	All Reviews Performed	All Cases Questioned
Admission	11,296*	100.00%	
Review Cases Questioned	92	0.80%	100.00%
1. Benefits terminated cases	5	0.04%	5.43%
2. Cases discharged without formal UR decision, but:			
a) Coordinator stated case was a Voluntary Early Discharge (Definite VED)	10	0.01%	10.87%
b) Physician contacted, patient discharged in <24 hours, but coordinator did not state case as a VED (Possible VED)	2	0.02%	2.17%
Extended Stay	11,455**	100.00%	
Review Cases Questioned	2,028	17.70%	100.00%
1. Benefits terminated cases	79	0.69%	3.90%
2. Cases discharged without formal UR decision, but:			
a) Coordinator stated case was a Voluntary Early Discharge (Definite VED)	48	0.49%	2.76%
b) Physician contacted, patient discharged in <24 hours, but coordinator did not state case was a VED (Possible VED)	26	0.23%	1.28%

* Admission Reviews Performed data missing for eight hospitals.
** Extended Stay Reviews Performed data missing for two hospitals.

It should also be noted that 45% of all extended stay reviews questioned during the study period had been previously questioned at an earlier date (not simply reviewed previously); 26% had been questioned at least twice before and in the most extreme instance, one patient's continued stay was questioned for the 27th time. A considerable portion of cases in which physician reviewers are involved—that is, those which are not automatically approved by the coordinator—are ones which have been previously questioned in the UR process.

Characteristics of Patients Whose Continued Stay was Questioned or Terminated as a Result of UR Actions

One of the most striking findings of this study were the age and diagnostic characteristics of patients whose stays were questioned and/or terminated. As shown graphically in Fig. 2, the average age of all questioned cases in the study was 62, while the age of the majority of all hospital patients in the United States is below 45. For the extended stay termination cases, the average age of patients was 79 and the median age of these cases was 83 years. Almost two-thirds of all questioned cases and 94% of all terminations occurred in Medicare patients, as might be expected with these age distributions. This finding cannot be attributed to a selective Medicare utilization review focus in our study hospitals, since approximately 75% of the hospitals were reviewing almost all age categoreis of patients and Medicare patients account for only 14% of the total admissions to Massachusetts hospitals.

The diagnostic and operative categories of patients whose continued stay in the hospital is questioned by UR committees showed a marked concentration in certain areas, as shown in Tables 4 and 5. Eight medical diagnostic groups—cancer, stroke, fracture of the arm or leg, heart failure, organic brain syndrome, skin infection, heart attack and intestinal infectious disease—accounted for 39% of all the cases questioned. The same eight categories account for only 11.4% of all admissions to United States hospitals, based on 41% of all discharges collected by the Commission on Professional and Hospital Activities. Only half of this difference can probably be attributed to the increased age of the population.

Similarly, a comparison of questioned cases by type of surgical procedure to reference populations requires examination of the age-corrected PAS distributions,

TABLE 3. *Number of Study Hospitals Having At Least One Termination and/or Voluntary Early Discharge In A Two-week Period*

No. Hospitals With:	Extended Stay Reviews	Admission Reviews	Extended Stay or Admission Review
Terminations	23	5	24
Definite VEDs	19	6	22
Possible VEDs	20	8	23
Terminations + Definite VEDs	32	9	34
Terminations, Definite and Possible VEDs	32	12	34

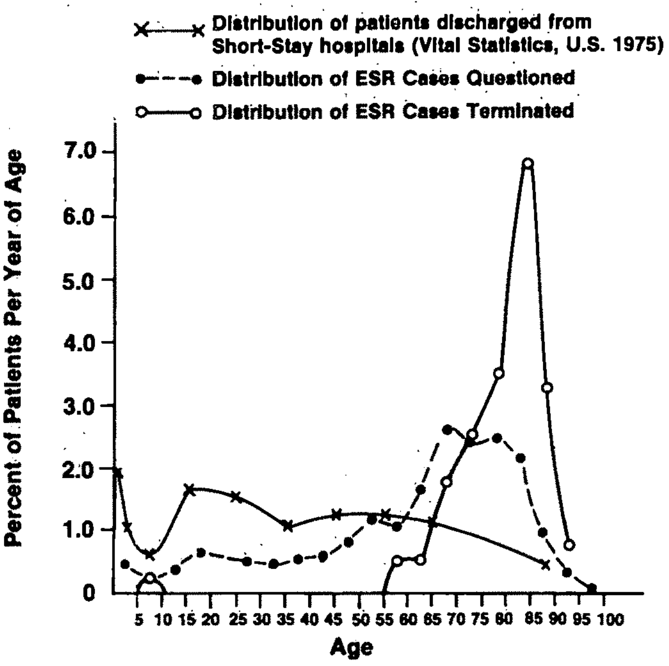

FIG. 2. Distribution of Patients Per Year of Age by Extended Stay Cases Questioned, Terminated, and Discharged from Short-Stay Hospitals. Line marked by crosses shows distribution of patients discharged from short-stay hospitals (Vital Statistics, U.S. 1975). Line marked by solid circles shows distribution of ESR cases questioned, and line marked by open circles shows distribution of ESR cases terminated.

because of the lower frequency of ENT, GYN, and obstetrical procedures in the elderly as compared to the general population. Even after such an age correction, however, it is clear that there are three categories of surgical procedures where the percentage of questioned cases is far higher than might be expected on a random basis. The percentage of neurosurgical cases was more than three times greater, the percentage of vascular and cardiac surgical cases was almost twice as great, and the percentage of the large orthopedic surgical group was almost 30% higher than what would be expected. Conversely, the percentage of urologic and of opthalmologic cases questioned were only half of what might be expected. While patients in the three "high" categories tend to have longer average lengths of stay than those of other surgical cases, this cannot explain a difference of this magnitude, since review norms are corrected for age and diagnostic distributions.

As noted in the section above, a large number of cases were questioned multiple times. Simple tests of association and multivariate analyses showed that surgical cases controlling for all other factors had a greater chance of being questioned more than once ($p < 0.01$) and a much greater chance of being questioned four or more times by the UR committee ($p < 0.001$). Other characteristics associated with being questioned multiple times were increasing patient age and whether the patient was admitted from a nursing home or a chronic disease facility.

Length of Stay of Terminated Cases

Of the 84 patients who had their benefits terminated during the two-week study period, 41 did not have a date for their discharge recorded by the end of the study. While the precise reason for this was not coded on the form, marginal comments plus debriefings of the coordinators who supplied the data indicated that, in almost all cases, the patients were still in the hospital after their three day "grace" period of continued coverage had expired. After that time, most had either became the financial responsibility of the Medicaid program or, at least in theory, had become "self-pay" patients. In fact, most of the latter group probably became bad debts for the hospital.

Of the patients who were discharged, almost half had lengths of stay which had already exceeded the 90th percentile adjusted for their age group and diagnosis when they left the hospital. Thus, while UR programs may have positive contributions to controlling total utilization of hospital days of care and produce average declines in length of stay, these changes are unlikely to be due to those patients whose benefits are terminated.

The Effect of UR Policies in Dealing with the Attending Physician

One set of systematic factors which could be related to the frequency of extended stay terminations and voluntary early discharges per 100 beds were the standing policies with regard to the contracts between the UR staff and the patients attending physician. As shown in Table 6, hospitals where coordinators had no restrictions placed on their dealings with the attending physicians and the UR committee mem-

TABLE 4. *Extended Stay Review Case Questioned: Most Frequent Diagnoses and Comparisons With National Distribution*

Diagnostic Category	ESR Cases Questioned	PAS* Total U.S. Average	PAS* Over 65 Average
Cancer	14.6%	3.8%	9.2%
Strokes	6.0%	1.4%	5.7%
Fractures: Arm & Leg	4.2%	2.2%	3.9%
Heart Failure	4.2%	0.9%	3.4%
Organic Brain Syndromes	2.6%	0.2%	0.7%
Skin Infections	2.2%	0.5%	0.5%
Heart Attack	1.5%	1.0%	2.3%
Intestinal Infectious Disease	1.5%	1.4%	1.0%
Total (Of these eight Categories)	39%	11.4%	26.7%

* Data from 41% of all U.S. discharges, collected by the Professional Activity Survey (PAS) of the Commission on Professional and Hospital Activities.

bers sometimes or always remained anonymous with respect to the attending physician when a case was questioned, had twice the rate of terminations and voluntary early discharges per 100 beds than did those hospitals where the coordinators were restricted and/or the physicians never attempted to be anonymous in the UR committees dealings with the attending; the difference in means was significant at the $p < 0.03$ level. Hospital size, teaching status and ownership showed no significant effects on the rate of terminations and voluntary early discharges.

TABLE 6. *The Effect of Restriction of UR Coordinator Authority and UR Physician Anonymity on Total Terminations and Voluntary Discharges Per 100 Beds*

Terminations Plus Definite and Possible VED's per 100 Beds	Mean ± S.E.	Significance of Difference in Means
1. Coordinators Unrestricted and UR Physicians Ever Anonymous	2.72 (± 2.07)	p < .03
2. Coordinators Restricted and/or UR Physicians Never Anonymous	1.29 (± 1.51)	

Discussion

If the findings in this case study are confirmed or otherwise proved to be general they have implications for the operation of UR activities which should be of interest to both policy makers, and physicians and surgeons in the United States. First, we have documented that "voluntary early discharges" occur regularly as a result of UR programs but probably not as often as some UR proponents have indicated.

Second, we have found that terminations occur more frequently than reported in previous case studies. A little over a year ago, McSherry published a report on the experiences of the New York Hospital-Cornell Medical Center with UR programs.[2] In this 1400 bed institution, an average of only six patients per year were identified where the UR committee had to intervene because of unnecessarily prolonged length of stay; the cost of identifying each patient was $34,212. McSherry stated: "In the university hospital, the active participation of the graduate (house) staff in patient care renders the requirements for certification/re-certification of the need for hospital services or admission review superflous." In this case study, which incorporated eight of the major teaching institutions in Massachusetts, the UR committee intervened at a rate which was thirty times greater than that reported at the New York Hospital-Cornell Medical Center, after correcting for average size differences.

TABLE 5. *Distribution of Surgical Cases Questioned by UR Committees by Type of Procedure Groups to National PAS Distribution (Total Population and Age ≥ 65)*

Surgical Procedure Groups	ESR Cases Questioned	PAS Total U.S. Average	PAS Over 65 Average
Obstetrical	0.8%	3.9%	0.1%
Oral/Maxillofacial	0.5%	0.3%	>0.1%
Neurosurgery	3.8%	1.1%	1.2%
Vascular/Cardiac	11.8%	3.4%	6.5%
Orthopedic	18.5%	11.0%	12.9%
Proctological	3.6%	2.5%	2.7%
Otorhinolaryngology	3.7%	10.5%	3.0%
Plastic Surgery	6.0%	5.7%	4.9%
Abdominal	20.0%	14.4%	19.1%
Thoracic	2.7%	1.0%	2.6%
Thyroid/parathyroid Thymus/adrenals	0.3%	0.5%	0.3%
Gynecological	2.7%	19.1%	4.7%
Biopsy/Diagnostic Other	3.4%	3.9%	6.7%
Ophthamology	5.8%	3.9%	6.7%
Urological	7.4%	7.3%	15.5%
Dental	0.3%	2.6%	0.7%
Breast	0.8%	3.1%	2.5%

In a national survey undertaken in parallel with this case study, Gertman et al.[1] found that hospitals in the northeastern region of the United States averaged 42 admission and extended stay terminations per year, confirming that the magnitude of terminations and possibly the other findings, of this case study may be general to hospitals in our region. Given that there were institutions, both in this case study and in the national survey, of the same size and complexity as the New York Hospital, the possibility must be raised that McSherry's findings were due to the lack of aggressive implementation of concurrent UR programs at his institution. As the Massachusetts data suggests, operational factors such as reviewing physician anonymity may be critical to aggressive UR action.

The importance of terminations as a measure of impact has been demonstrated in a recent analysis of Medicare utilization pattens and hospital termination activities by Gertman et al.[3] They have found that those hospitals that had one or more admission terminations in 1976 had an *absolute decline* in the total days of care provided to Medicare patients between 1974 and 1976, while those with no admission review program (and/or a review program without terminations) had an absolute increase. Based on an HEW estimate that the variable savings per a one day decline in Medicare usage equals $60, the utilization difference of 1,049 days/year/hospital represents a benefit of $62,924 per year, an amount which far exceeded the cost of operating review programs in these institutions.[1,4] Extended stay terminations also had a small effect on decreasing Medicare usage, after controlling for other factors. This data suggests that while terminating cases of prolonged stay may not significantly alter average length of stay, aggressive self-policing programs may be having a significant effect on total Medicare utilization.

Third, questioned cases, particularly upon extended stay review, appear to be disproportionately chronically ill medical patients and surgical patients, such as neurosurgical and cardiovascular cases who frequently have prolonged and complicated postoperative recuperation and rehabilitation needs. In theory, prolonged care for these cases can be provided at a lower level of care than an acute hospital. Unfortunately, however, first class facilities and the mechanisms for paying for care in them are frequently inadequate. While effective UR programs which move people out of the hospital into their homes or subacute institutional arrangements may contribute to holding down hospital costs, some of these may be offset by increased Medicare and Medicaid expenditures for nursing home care. Also, such calculations do not count the financial and emotional costs of alternative care arrangements to patients and their families.

Finally, the study shows that hospital UR programs, while effective for Medicare, may have little direct impact on Medicaid patients and private insurance beneficiaries. An evaluation of the New Mexico Medicaid EMCRO programs operations from 1971 to 1973 found only 87 admission and extended stay denials during a full two-year period, a rate per hospital of less than one per year compared to the one per week in this Massachusetts case study.[5] Both studies tend to raise serious questions about the value of concurrent review of all Medicaid admissions. In Massachusetts, the leading causes of admission in the Medicaid population are normal deliveries and illnesses of children. It is not surprising that Medicaid concurrent review appears to have little payoff, since one would expect few "unnecessary admissions" or prolonged lengths of stay in these patients. It might be far more cost effective to monitor Medicaid utilization through aggregate profiles of utilization patterns for common diagnoses, using case-by-case review only as a standby mechanism to be implemented for identified problems.

The usefulness of UR for private insurance beneficiaries, particularly employed adults, may be more complicated than would first appear, from the results of the study. Utilization problems in this population of patients are probably not of the prolonged, chronic disease type, but rather relate to the necessity of admission and provider inefficiencies in not discharging the patient a day or two earlier. Most current utilization review programs for private insurance patients are voluntary on the part of hospitals; they are not supervised by outside agencies such as a PSRO or a state Medicaid program, and thus, "hospital-initiated" UR of such patients may be relatively ineffective. Data is beginning to accumulate, however, that "physician initiated" UR for private insurance beneficiaries in fee-for-service HMOs (or "individual practice associations") may lead to marked declines in days of hospital care per thousand enrollees, particularly when the plan involves some element of risk-sharing for the physicians.[6] Thus, there may be: 1) variation in the type of review which needs to be performed for different patient groups, 2) differential effectiveness depending on the locus of control for the review program, and 3) differential impacts of the way in which reviewing physicians relate to their peers. Further investigation of these factors may assist in defining more effective mechanisms for controlling the rise in health care cost.

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DISCUSSION

DR. CHARLES K. MCSHERRY (New York, New York): In 1976, I discussed the subject of utilization review before the Society of University Surgeons. At that time, I pointed out that at The New York Hospital we were reviewing approximately 10,000 patients per year to identify six per year with unnecesarily prolonged lengths of stay. The cost of identifying these patients was in the neighborhood of $34,000 per patient.

Dr. Egdahl's paper presents a new light and perspective on utilization review. In his study, utilization review intervention is about thirty times more frequent than my intervention at The New York Hospital. Furthermore, the number of patients whose continued stay was disapproved of is about eight times higher than the incidence I predicted. Undoubtedly the major factor for this discrepancy is the individual doing the reviewing. In Dr. Egdahl's study, nurses were employed for the review, and since their salary was dependent on the effectiveness of utilization review, they were no doubt more stringent in their reviews than I was.

In this manuscript, Dr. Egdahl suggests that about $63,000 per hospital was saved by utilization review. I would submit, however, that these savings may be more illusory than real. I wonder if we are not talking about a redistribution rather than a saving of the health care dollar. Money saved at the hospital level may well have been expended at the nursing home level. Finally, I would comment on the financial impact to the hospital of utilization review. When a patient's continued stay is disapproved, the financial burden falls on the hospital rather than the patient. Most of the patients who have had their stay cancelled end up as bad debts to the hospital rather than self-paying patients. It is unfair to the hospitals.

Dr. Egdahl's study points out some of the areas that are least cost-effective in terms of utilization review, namely admission review and the review of certain urologic and ophthalmologic operations. In my study of utilization review, I also pointed out areas that were not cost-effective. I would like to ask Dr. Egdahl if he feels there is any opportunity for bringing about meaningful changes in utilization review in areas that are not cost-effective. If this were possible, we might achieve a reduction in the cost of utilization review.

Dr. Ben Eiseman (Denver, Colorado): One major problem in efficient utilization of hospital beds is that it works counter to the economic interests of the hospital. It is equivalent to asking a luxury hotel manager to urge his tourist guests to cut short their vacation from a week to five days. Cutting down patient days similarly decreases income of the hospital. This is particularly important in an overbedded community where hospitals strive to bring up their census.

Dr. George D. Zuidema (Baltimore, Maryland): I have four questions which I would like to ask, because I think that a further consideration of some of these other points may have some relevance to the picture which Dr. Egdahl gave us today.

First of all, how many of these hospitals had preadmission review to determine the appropriateness of the admission in the first place? Some years ago, when this type of system was instituted in Maryland, there was a significant drop in hospital admissions right at the very beginning, and it had a later effect, of course, in terms of the necessity of keeping those patients in the hospital.

The second question is: How long had the various utilization review programs been in effect? In other words, had the programs been going long enough to have given the hospital staffs a learning curve, so to speak, or are they on the early part of the curve, where they are just beginning to get experience with utilization review?

Third, was it possible to correlate the availability of social services and extended care facilities with the various types of problems encountered in the hospitals?

Finally, did you detect any variation among various types of hospitals and staff which you studied?

Dr. Richard H. Egdahl (Closing discussion): Dr. McSherry raised a lot of points. As far as the nurses are concerned, no termination is carried out without the approval of the M.D. reviewer.

Savings occurred only in those hospitals with at least one admission termination per year. Since the cost of operating UR programs in these hospitals averaged $49,196, the *net* benefit was only $13,728 per year. In the many hospitals without admission terminations, there were no measurable savings.

Whether the savings go to the nursing homes as a redistribution of funds, I don't know, but I doubt it. I think the best evidence is that, although there may be some extra nursing home admissions, and some societal costs where a member of the family has to stay home and take care of people who were discharged before they were fully able to take care of themselves, they do not match the savings. Cost studies of this sort are hard to do and are almost nonexistent.

Selectivity in utilization review was mentioned and this is a very important point. Probability profiling of selected high-target situations in Medicaid, populations, for example, would be a good approach, because the most common admissions for Medicaid were for normal deliveries and for children with infections. We're not going to expect a lot of overutilization, in general. So that's a target, I think—selective profiling—for the future.

Dr. McSherry asked, "How do we get changes in utilization review?" This gets back to what we are reading now about HMO's, and was the basis of the paper I gave here last year and also is the theme of speakers this morning on health insurance. If we assume that we can continue in our present situation by just being high quality surgeons and practitioners, while the costs continue to go up at the rate they are now, we're going to be in trouble.

What can we do ourselves? It seems apparent that government mandated utilization review and Blue Shield utilization review, as it has been carried out in the past, haven't been adequate. What does work, it seems, is when physicians set up organizations and develop profiles, set criteria, and do utilization review themselves. Even under those circumstances, there probably has to be some financial risk-sharing.

Significant changes in utilization result when this is done across the board, involving all categories of patients. If, indeed, you study where you can achieve effective utilization review, which you do not have in our present health system for the most part, you get it for older people, and the societal costs there are questionable.

We then come to the basic question asked by both Dr. Eiseman and Dr. McSherry: what happens to the hospitals? If we're overbedded in an area, as Dr. Eiseman said, what can the community do?

The answer appears to emerge out of the experiences of some places where they have set up effective risk-sharing fee-for-service HMO's. The hospitals phase down to a new size and efficiency.

However, an interesting editorial in the *New York Times* a few weeks ago by Dave Kendig made the point that groups which are overrepresented as hospital employees, including many blacks and Puerto Ricans, will lose their jobs if hospitals beds are phased down. A critical feature is that in certain metropolitan areas, as hospital beds are closed, we've got to be sure that jobs that are lost are replaced in some way.

In some areas of the country, such as Wausau, they have an effective fee-for-service HMO and an appropriate number of beds. In some other areas of the country, where utilization review is working, there has been a shrinkage. We seem to be grossly overbedded in some areas of the country. Kaiser gets by with around two beds per thousand; the nation, between six and twelve. There are many places where it's seven and eight: National Health Planning guidelines suggest four beds per thousand. We're simply holding out on the basis of community convenience, and what's going to have to happen is that some areas will continue to have more beds than appear to be needed because of local pressure.

Dr. Zuidema asked four questions. How many had preadmission review? None, to the best of my knowledge. The Minneapolis fee-for-service HMO dropped their days of hospitalization from around 850 to 550 days per thousand by a rigorous peer review system including preadmission certification.

How long have the programs been in effect? Variable periods of time. I think he's right that as time passes, there may be an increase in effectiveness, but I think effectiveness is far more dependent upon variables such as physician anonymity, and nurse reviewer capabilities then upon how long the program has been in effect.

Can you correlate social services with the discharges? This is what we're trying to do now. It's a bear of a study, because it means you've got to talk to each person that's been involuntarily or voluntarily early-discharged, and find out where they went and how much it cost, and put that against the savings that occurred in the hospital. It's a very complex form of health services research.

The other question centered around variations in the types of hospitals and their staffs. As far as we could see, it didn't matter whether it was a teaching hospital, how big a staff was present, how large a hospital it was or whether it was municipal or nonprofit. The only variable we found that really seemed to make a difference was whether the physicians tended to remain anonymous in the process and whether the nurse reviewers had a fair degree of latitude.

The Use of Silastic Transhepatic Stents in Benign and Malignant Biliary Strictures

JOHN L. CAMERON, M.D., BOB W. GAYLER, M.D., GEORGE D. ZUIDEMA, M.D.

Between 1969 and 1978, 45 patients with biliary strictures have been managed surgically utilizing silastic transhepatic stents. In 25 patients the strictures were benign. After resection or dilatation of the benign stricture, an hepaticojejunostomy was performed to a Roux-en-Y loop. The anastomosis was stented with a large bore silastic tube with multiple side holes passed through the biliary tree, out the anterior surface of the liver, and then out through the abdominal wall. There was one hospital death. Most stents were left in place for one year. Of the 15 patients with long-term follow-up, all have had excellent results.

In 20 patients the strictures were malignant and involved the common hepatic duct in 10 patients or its bifurcation in 10 patients. In 14 patients the tumor was thought to be primary in the biliary tree, and in six patients the tumor was felt to represent a metastasis or direct extension from another site. In three patients the tumors were resected, and in the remaining they were dilated or bypassed. After positioning a silastic transhepatic stent, a hepaticojejunostomy was carried out. There were two hospital deaths. Serum bilirubin on admission averaged 17.1 mg%, and after decompression 1.8 mg%. Five patients have survived over one year, and two over two years. Postoperative radiotherapy and a primary biliary tumor favored longer survival.

BENIGN AND MALIGNANT strictures of the biliary tree present difficult problems in management. Benign strictures are usually high in the hilum of the liver and difficult to expose, a mucosa-to-mucosa anastomosis hard to achieve, and late recurrences disappointingly frequent. With malignant biliary strictures involving the common hepatic duct or bifurcation, resection is usually not possible. Such patients die, not from the slow growing biliary tumor, but from hepatic failure due to biliary obstruction which is difficult to adequately and permanently decompress.[5] A technique used over the past nine years to manage such patients utilizes a silastic transhepatic biliary stent. Despite the different problems that benign and malignant strictures present, the use of this technique of transhepatic intubation with a silastic stent has markedly improved the management of both groups of patients.

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Clinical Material

Forty-five patients with biliary strictures have been managed with silastic transhepatic biliary stents at The Johns Hopkins Medical Institutions between 1969 and 1978. In 25 patients the stricture was benign and in the remaining 20 patients it was malignant.

Benign Strictures

The ages of these 25 patients ranged from 18 to 75 years and averaged 42 years. Twenty were females and five were males. The etiology of the benign stricture was surgical trauma in 21 patients, a gun shot wound to the porta hepatis in one patient, congenital cystic dilatation of the biliary tree in one, a benign cystadenoma in one, and an idiopathic inflammatory process in one. The stricture involved the common hepatic duct in 21 patients and the bifurcation of the hepatic duct in four. For 13 patients the current procedure was the first attempt at repair of their benign stricture. Seven patients had undergone one prior repair, four had two prior repairs, and one patient had undergone four prior repairs. Serum bilirubin at the time of admission ranged from 0.4 mg% to 19.3 mg%, and averaged 7.4 mg% (Table 1).

Malignant Strictures

The ages of these 20 patients ranged from 43 to 82 years and averaged 61 years. Thirteen were males and 7 were females. In ten patients the malignant stricture involved primarily the common hepatic duct. In the remaining ten patients the tumor occurred at the bifurcation. In 14 patients the tumor was felt to be primary in the biliary tree. However, this was often difficult to determine and in some instances the tumor could have originated in the pancreas or elsewhere. In

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Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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TABLE 1. *Biliary Strictures in 45 Patients*

Biliary Stricture	Patients	Age (Yrs.)	Sex (M, F)	Stricture Site		Serum Bilirubin (mg%)
				CHD	Bifurcation	
Benign	25	42	20F, 5M	21	4	7.4
Malignant	20	61	7F, 13M	10	10	17.1

the remaining six patients the malignant biliary stricture was felt to represent direct extension or metastatic spread from a tumor in the colon (three patients), stomach (one patient), gallbladder (one patient), or pancreas (one patient). One of the patients who had a primary biliary tract tumor involving his bifurcation had a long history of ulcerative colitis. Serum bilirubin at admission in these 20 patients with malignant biliary strictures ranged from 4.9 to 36.9 mg%, and averaged 17.1 mg% (Table 1).

Operative Management

Most patients prior to surgery had their biliary tract anatomy defined by transhepatic, endoscopic retrograde, T tube, or sinus tract cholangiography. All patients were started on Penicillin and Gentamycin the night prior to operation.

Benign Strictures

Twenty-four of the 25 patients with benign strictures had their repair performed in the hilum of the liver. In 16 patients the stricture was resected. In eight instances the stricture was so high in the hilum or the parenchyma of the liver that it was not resectable, and was dilated with Bake's dilators. The final patient had an intrahepatic cholangiojejunostomy (Longmire Procedure) performed at the periphery of the left lobe of the liver.

After the stricture was resected or dilated, a curved stone forceps was introduced into the biliary tree and advanced either through the right or left intrahepatic duct until it could be brought within a centimeter or two of Glisson's capsule on the anterior superior (diaphragmatic) surface. The forceps were then forcibly advanced out through the liver parenchyma. A silastic biliary stent was sutured to the end of the forceps and drawn back down through the liver parenchyma, intrahepatic biliary tree, and out the hilum of the liver (Fig. 1). The silastic biliary stents are 60 cm in length and come in three outside diameters: 10 mm, 8 mm, and 6 mm. Forty per cent of the length of the silastic stent contains multiple side holes.* The largest stent that will be accommodated by the dilated biliary tree is used. Generally it is one of the two larger sizes. In 15 patients with benign strictures the stent was placed in the right hepatic duct. In eight patients, including the one undergoing a Longmire Procedure, the stent was placed in the left hepatic duct. In two of the patients with strictures involving the bifurcation of the hepatic duct, stents were placed in both the right and left hepatic ducts (Table 2). Once the stent is in place, a Roux-en-Y loop is fashioned and placed in the hilum. The end of the loop is closed and an end-to-side hepaticojejunostomy performed. In most instances a mucosa-to-mucosa anastomosis cannot be fashioned. After the biliary stent is placed into the jejunum through a stab wound, the Roux-en-Y loop is sutured to the hepatic duct, liver capsule, and other hilar structures surrounding the biliary stent. A large mattress suture is then placed around the exit site of the stent on the anterior surface of the liver. This end of the tube is brought out through a stab wound in the upper abdomen and connected to bile bag drainage (Fig. 2). Penrose drains are left to drain the exit site of the stent on the anterior surface of the liver, and the anastomosis. Postoperatively, the biliary stent is left to gravity drainage until a cholangiogram demonstrates that the anastomosis and exit site on the liver have sealed. The Penrose drains are then removed and the stent clamped. Thereafter, the patient irrigates the transhepatic stent twice a day for as long as it remains in.

Malignant Strictures

Operative management of the 20 patients with malignant strictures was very similar to those with benign strictures. In three patients, two with tumors at the bifurcation and one with a tumor in the common hepatic duct, resection was performed. In all three patients positive tumor margins in both ducts were left on the liver side. In 16 patients the tumor was dilated by passing instruments up from normal duct below the tumor, or else the biliary tree was entered via the left or right hepatic duct above the tumor (Fig. 3). One patient had an intrahepatic cholangiojejunostomy (Longmire Procedure) performed away from the tumor and hilum of the liver. After access to the intrahepatic biliary tree was achieved by resection, dilatation, or entering above the tumor, a

TABLE 2. *Silastic Transhepatic Tube Placement*

Biliary Stricture	Patients	No. Stents			Location of Stents			
		1	2	3	R Duct	L Duct	Both	3 Ducts
Benign	25	23	2	0	15	8	2	0
Malignant	20	14	5	1	6	8	5	1

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* Dow Corning

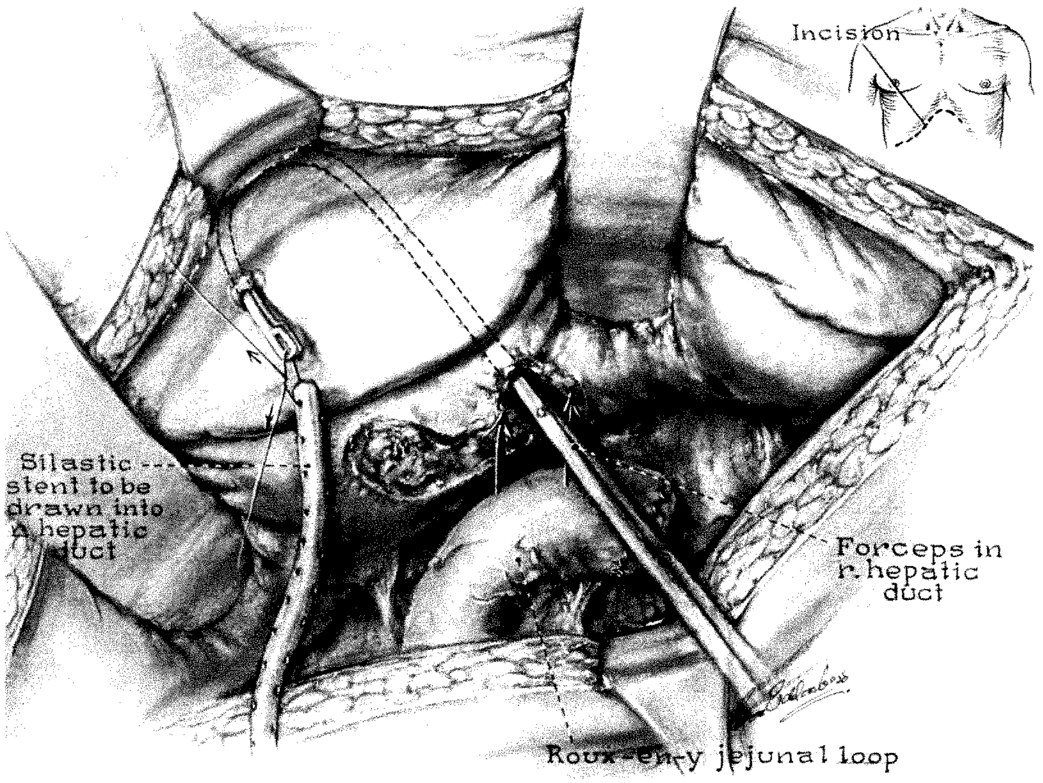
Incision
Silastic stent to be drawn into r. hepatic duct
Forceps in r. hepatic duct
Roux-en-y jejunal loop

FIG. 1. Stone forceps have been passed into the common hepatic duct at the hilum, advanced through the intrahepatic biliary tree, and forced out through the parenchyma on the anterior surface of the liver. A silastic biliary stent is then sutured to the end of the forceps so that it can be drawn back into the intrahepatic biliary tree and out the hilum.

transhepatic biliary stent was inserted in a fashion identical to that for benign strictures. In 14 patients one transhepatic stent was placed. In eight instances the single stent was placed in the left hepatic duct and in six patients it was placed in the right hepatic duct. Five patients had biliary stents placed in both the left and right hepatic ducts. The final patient, after tumor resection, was left with three large open ducts, and transhepatic stents were placed in all three (Table 2). In four patients, once the silastic stent was inserted, it was passed into the duodenum through the common duct, after performing a sphincteroplasty. In the remaining 16 patients a Roux-en-Y loop was constructed and a hepaticojejunostomy performed. In many instances the jejunum was sutured to tumor surrounding the egress site of the silastic stent in the liver hilum. The tumor margins were marked with hemoclips for possible radiotherapy (Fig. 4). The stent exit site on the liver and the anastomosis were drained and the stent managed in a fashion identical to that described for benign strictures.

Clinical Course

Benign Strictures

One patient died following repair of a benign stricture. She was a 67-year-old-woman with a biliary stricture of 20 years duration and biliary cirrhosis. She had undergone two prior attempts at repair. She tolerated the operative procedure but died in the hospital 65 days later of liver failure. Hospitalization in the remaining 24 patients ranged from eight to 70 days, and averaged 31 days. All patients developed biliary-cutaneous fistulas at the exit site of the biliary stent from the liver and/or from the anastomosis. All fistulas closed spontaneously but often took two or three weeks and resulted in the long average hospitalization. Four patients developed wound infections following surgery. Three patients required drainage of an intra-abdominal abscess. Two patients developed sepsis during the first week after surgery, presumably from bile leaks.

There have been two late deaths. Both patients died of sepsis during sodium cholate infusion into their transhepatic stent. Both patients had tolerated their operative procedures well and were asymptomatic. At eight months following their repair both were readmitted for sodium cholate infusion because of retained intrahepatic biliary sludge that had not been successfully cleared from the biliary tree at the time of repair. Shortly after the infusions were started both became hypotensive and died. Positive blood cultures were obtained in one.

The remaining 22 patients are alive and well. In most patients the silastic transhepatic stent was left in for 12 months and then removed. Initially the tubes were changed during this 12 month period only if they

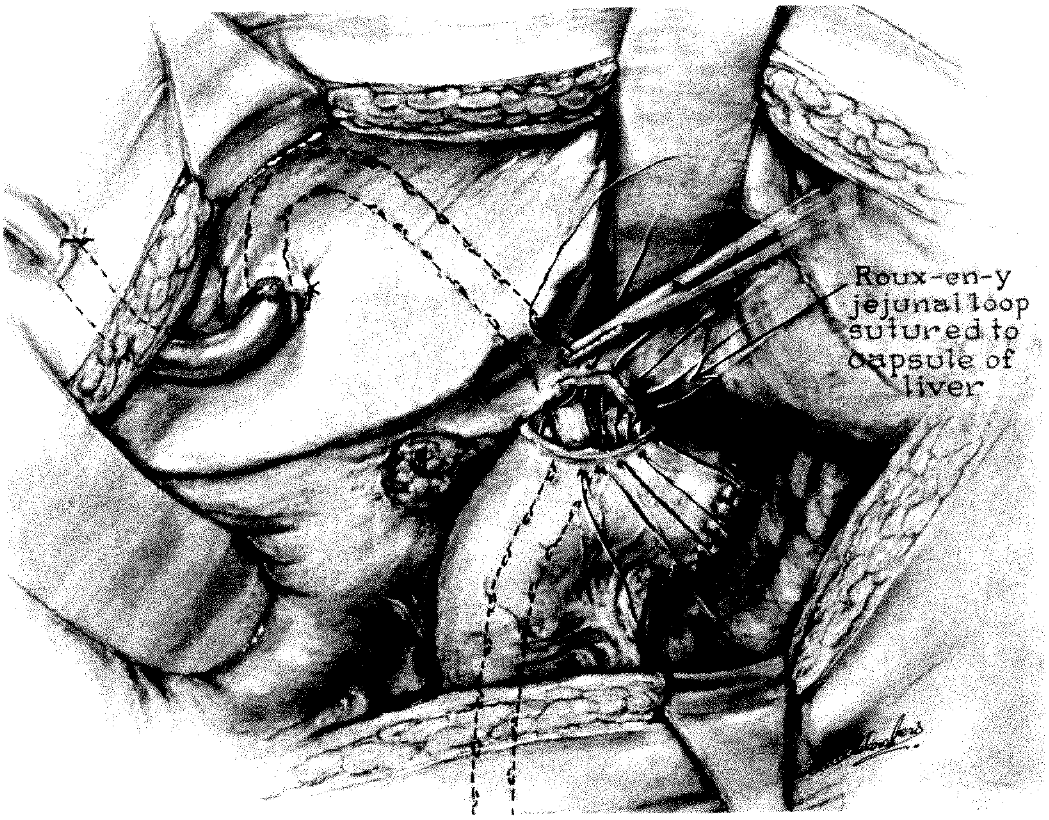

FIG. 2. A Roux-en-Y jejunal loop is sutured to hepatic duct, liver capsule and other structures at the egress site of the silastic stent in the hilum of the liver. That portion of the stent that passes through the liver and into the jejunum contains multiple side holes.

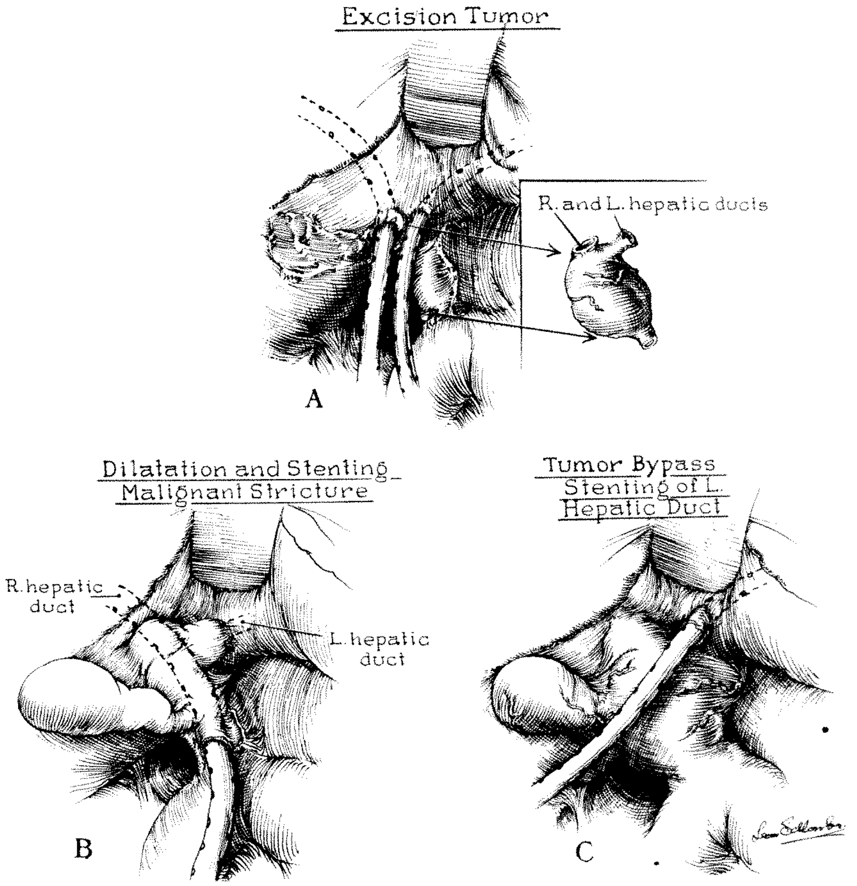

FIG. 3. When dealing with malignant biliary strictures, the lesion is either resected (A), dilated from below (B), or bypassed (C) by entering the right or left hepatic duct above the tumor. Silastic stents are then placed in a fashion identical to that for benign strictures.

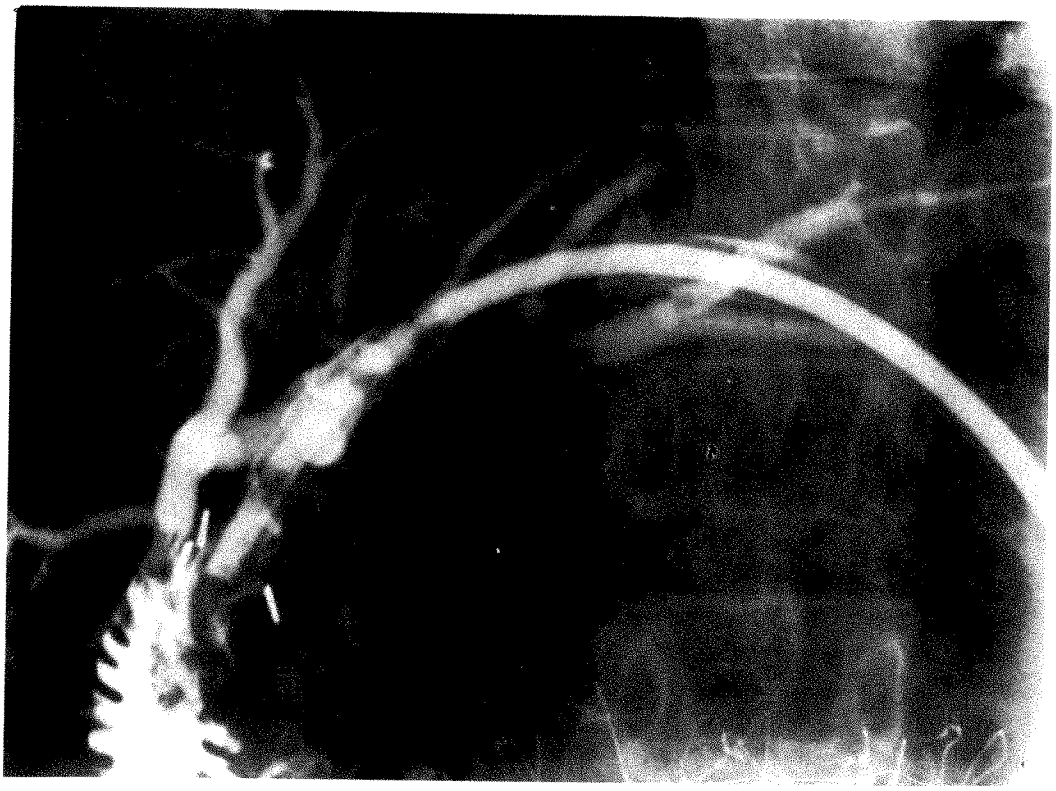

FIG. 4. Postoperative cholangiogram of a patient who underwent dilatation of a malignant stricture with the placement of a silastic stent into the left hepatic duct. Hemoclips mark the tumor for the radiotherapist.

became partially occluded. Recently we have been routinely changing all stents every three months to avoid partial occlusion with leakage around the stent cutaneous exit site and/or fever. These tube changes can easily be performed under fluoroscopy as an outpatient procedure. A guide wire is threaded through the silastic stent into the Roux-en-Y loop. The stent is then removed leaving the guide wire in place. The new silastic transhepatic stent is then easily threaded back in place over the guide wire, which is then removed.[2] Twelve patients have had their tubes removed permanently and have been followed an average of four years and 11 months (12–108 months). All 12 are classified as excellent results. Eleven have remained asymptomatic and with a normal serum bilirubin. The twelfth patient became jaundiced from a stricture recurrence six years and ten months following his initial repair. He was reoperated upon and a silastic stent reinserted after dilitation of the stricture. The transhepatic stent was left in for 16 months. He has now been followed for two years and two months since his second repair and remains asymptomatic.

In three additional patients followed for an average of two years and two months (15–42 months) the silastic stents remain in place. Because of the difficulty of the repair, it is not anticipated that the stents will be removed. They are changed in outpatient radiology every three to six months. All three patients are asymptomatic. Two patients have normal serum bilirubins, and the third has a mild elevation. All three are classified as excellent results.

The final seven patients have all been operated upon during the last 12 months. The stents remain in place. It is anticipated that they will be removed in all seven patients at 12 months. All are asymptomatic (Table 3).

Malignant Strictures

Two patients died following surgery for a malignant stricture. One patient, a 66-year-old male with a biliary tumor at the bifurcation, died of sepsis 30 days after surgery. A stent was placed in his right hepatic duct, but because of tumor his left duct could not be decompressed. Cholangitis in his occluded left duct could not be controlled with antibiotics. The second death occurred in a 62-year-old man with a tumor at his bifurcation. Ten days after surgery he suddenly became septic and died. Subphrenic and subhepatic abscesses were found. Hospitalization in the remaining 18 patients ranged from seven to 77 days and averaged 30 days. Two patients required drainage of an intra-abdominal abscess. One developed postoperative sepsis and one patient developed a wound infection. After biliary decompression the average serum bilirubin dropped from an admission value of 17.1 mg% to 1.8 mg%.

TABLE 3. *Surgical Results of Patients with Benign Strictures*

Patients	Operative Deaths	Late Deaths	Results < 12 Months		Results > 12 Months	
			Excellent	Poor	Excellent	Poor
25	1	2*	7	0	15	0

* Secondary to sodium cholate infusion.

TABLE 4. *Effect of Radiotherapy and Site of Origin on Survival in 12 Patients Dying with Malignant Biliary Strictures*

	Patients	Average Survival (Mos.)
Late Deaths	12	11
Radiotherapy		
Yes	7	12
No	5	7
Malignant Strictures		
Primary	6	15
Secondary	6	7

Twelve of the 18 patients who were discharged from the hospital have died. Two lived for over two years, one lived for over one year, three died between seven and 12 months following surgery, and six died within the first 6 months of surgery. Average length of survival in these 12 patients was 11 months. In the seven patients who received radiotherapy survival averaged 13 months as compared to 7 months in those five patients who received no radiotheapy. Six of the 12 patients who died were felt to have primary biliary tract tumors, and survival in this group averaged 15 months. In the six patients with secondary malignant biliary obstruction, survival averaged 7 months (Table 4). Of these 12 patients who survived the operation and were discharged from the hospital, eight died as a result of their tumor, and not from biliary obstruction. Two patients were not adequately decompressed and one died of sepsis at three months, and the second of hepatic failure at six months. The cause of death in the remaining two patients is not known.

Six patients remain alive. Two have survived more than one year, two are alive seven to 12 months following surgery, and two have been operated upon during the past six months (Fig. 5).

Discussion

The technique of transhepatic intubation was described by Goetze[4] in 1951 and by Praderi in 1961.[10,11] Subsequently, Smith popularized this technique of biliary stenting,[13] and reported his experience with benign strictures in 1975.[18] Saypol and Kurian[12] in 1969 introduced the modification of a U tube transhepatic stent, and in 1972 Terblanche, Saunders, and Louw[15] extended this to malignant strictures. The technique of transhepatic intubation using a silastic stent has been utilized in our clinic since 1969. An initial report on this technique in ten patients was reported in 1976.[2] The silastic stent has distinct advantages in the management of both benign and malignant biliary strictures, and we feel is responsible for improvement in longterm results.

Over the past decade the surgical management of benign strictures has become fairly standardized. Most surgeons feel an anastomosis between the proximal hepatic segment and a Roux-en-Y jejunal loop is preferable to one using the duodenum or distal bile duct.[6,16] Whether or not to use a biliary stent is somewhat more controversial but many surgeons advocate their use in difficult repairs.[6,16] However, even with these techniques utilized in the most prominent clinics, longterm success is generally achieved in only 65% to 80% of patients.[3,16-18] Most benign strictures occur high in the hilum of the liver and are close to or involve the bifurcation of the common hepatic duct. An anatomical repair with good mucosa-to-mucosa approximation is always preferable, but often impossible. The technique of repair for benign strictures described here does not depend upon mucosa-to-mucosa approximation. After placing a biliary silastic stent transhepatically the jejunal loop is positioned around the egress site of the tube high in the hilum of the liver. During the ensuing weeks and months the gap that may exist between the mucosal surfaces will be bridged with epithelium. The scar that also forms will do so in the environment of the relatively nonreactive silastic stent with a minimum of

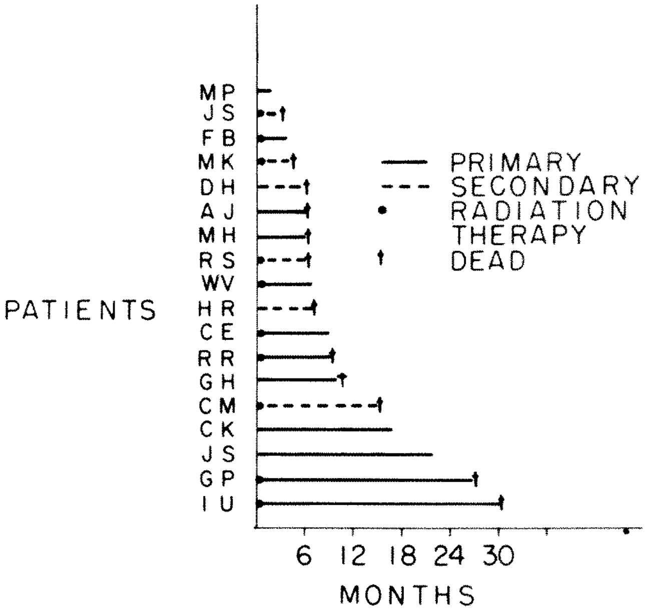

FIG. 5. Clinical course of the 18 patients with malignant biliary strictures who survived surgery.

foreign body reaction. As scar contracture occurs the anastomosis will be maintained widely patent by the large bore stent. At the end of a 12-month period, with the tract well epithelialized and a stable scar, the stent can be removed. In the interim the biliary tree and anstomosis can be kept free of biliary sludge by daily irrigations. Changing the tube every three months further insures against sludge collection and partial obstruction. Tube changes can be performed in ten minutes as an outpatient procedure.[2] The tube also provides access for cholangiography. Utilizing this technique of repair, virtually all patients with benign strictures have been managed successfull. The only two late deaths were probably related to sodium cholate infusions. Even though bile salt infusion into the biliary tree is effective and tolerated well through a T-tube, its use with a transhepatic stent infusing the solution directly into the liver is dangerous and should be avoided.[9] All 12 patients who have had their stents removed have had excellent results. The one recurrence (six years and ten months after the initial repair) was successfully treated by a second intubation. Smith has advocated a "mucosal graft technique" pulling the Roux-en-Y loop up into the liver with the transhepatic tube.[18] He has not used silastic and generally leaves the stent in place for only three to four months. His success rate has been 65%. We feel the use of a silastic stent left in for one year is important. If the repair is particularly tenuous, and a major duct has not been intubated, the stent may be left in permanently. We have recognized no adverse consequences of leaving the stent in over long periods in the three patients so managed (15, 21, 42 months). This technique of stenting can also be extended for use in the Longmire Procedure, when the hilum of the liver is no longer safe to dissect.[1]

Malignant biliary strictures present a different set of problems. If the tumor is primary in the biliary tree it often will be slow growing and slow to metastasize. Recognition of these tumors, first well described by Klatskin,[5] is often delayed. When the diagnosis is finally confirmed deep jaundice may be present and the patient often dies of hepatic failure. Ideally, such tumors should be recognized early and resected. However, because of the close proximity to the hepatic artery and portal vein, and the right and left intrahepatic ducts, local extension usually makes the tumor unresectable. Extended operative procedures including partial liver resection have been advocated and performed,[7] as has liver resection and allotransplantation.[14] However, currently, these procedures carry operative and late mortalities that argue against their routine use. Thus, for most patients with biliary tract tumors, effective biliary decompression is what is needed. The large bore thick walled silastic stents are very effective in this task. The average serum bilirubin on admission of 17.1 mg% dropped to 1.8 mg% after decompression. This allows effective palliation so that the patient's subsequent course will be determined by the malignant tumor, and not by the biliary obstruction. As adjuvant therapy improves, the palliation achievable should also improve. In our series the addition of radiotherapy to transhepatic intubation doubled survival time. Because of the small numbers, however, this difference was not statistically significant. Of the 12 patients felt to have primary biliary tract tumors who left the hospital, four lived or are still alive one year after surgery, and two lived over two years. Average survival of the patients with primary biliary tract tumors who have died was 15 months.

Secondary malignant biliary strictures, with the tumor arising outside of the bile ducts, is often a more rapid process. The colon, pancreas, or gall bladder malignancies from the biliary obstruction arises is often rapid growing, and death occurs from the tumor before hepatic failure is a problem. Occasionally, however, such a patient will remain relatively healthy despite disseminated tumor, and will be a suitable candidate for biliary decompression. The use of a silastic transheptic stent affords a relatively simple, rapid means of effecting this decompression. Palliation is usually somewhat shorter, however, because of tumor growth elsewhere. Our data suggest that survival after successful transhepatic stenting is only half as long with a secondary malignant stricture (7 months) as with a primary malignant stricture (15 months).

Silastic transhepatic stents were placed in only one duct in 14 patients with malignant strictures. In the remaining six patients both major ductal systems were drained. Ideally, both ducts should be intubated to avoid obstruction and sepsis. Drainage from both ducts is not needed to control the serum bilirubin. Longmire[8] has pointed out that decompression of one lobe is sufficient to maintain normal liver function. However, if infection occurs in the undrained duct it will not be controllable with antibiotics. One hospital death and one late death in our series were attributable to sepsis in an undrained duct.

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DISCUSSION

DR. JOHN TERBLANCHE (Cape Town, South Africa): I'm going to address myself mainly to the second half of this excellent paper which I enjoyed very much indeed.

(Slide) In doing so, I wish to make a plea to the members of the Association for the use of the U-tube, as depicted here. There are some technical differences since the last publication from our group of the use of this tube. We now use a long Argyle "Levine" type nasogastric tube. This is longer than the tube originally described and leaves you with long ends, which makes it easy to work with. We believe a firm tube is important. We have actually had a tumor constrict a Silastic tube and had to replace it for that reason. You will notice that we use only one hole above and one hole below the lesion. Bile drains through the tube and on into the duodenum. The U-tube does not produce an external biliary fistula.

(Slide) The tube is firmly fixed with a cross-piece, and I believe this is important and an advantage. We've actually had the problem of transhepatic tubes falling out, and this cross piece certainly holds the U-tube in place. In addition, when a transhepatic tube does fall out, if one doesn't replace it early, in our experience, it can be difficult to replace. This, I think, is a particular advantage of the U-tube procedure.

Recently, we have converted the U-tube to a circle O-tube, as soon as the patient is stable postoperatively. In other words, the two external limbs are joined together, and one has a completely closed system whereby the bile from either side will flow back into the patient without problems.

I would like to put the history of intubation of both benign and malignant strictures into perspective, as I believe this has not always been clearly defined. (The references will be published in Surgery Annual, Volume XI.) With regard to benign strictures, transhepatic intubation was first described by the two Mexican surgeons, Quijano and Munoz, in 1957 and 1959. Rodney Smith's classic paper in 1964, which was the first in the English literature, really started people using this technique for strictures.

As far as the U-tube's use in strictures is concerned, the first reports were in 1951 and 1959 by Goetze, the German surgeon, in the German literature. The most widely quoted paper is that of Saypol and Kurian in the American literature in 1969. However, Heydenrych, of South Africa, in a largely ignored paper, also described the use of the U-tube in biliary strictures in the same year in the American literature. Unlike Saypol, he had, in fact, already changed one of these tubes in a patient. I personally believe that a combination of the U-tube with Rodney Smith's mucosal graft procedure, as originally described by Goetze in 1951, has revolutionized our management of really high strictures. This makes the lesion very easy to handle technically.

With regard to bile duct carcinoma, the pioneering paper on dilatation and local intubation was, of course, published by Dr. Altemeier, of this society, in 1957. Transhepatic intubation was first described in the Uruguayan literature by Praderi in 1961, and he reported it in the English literature in 1974.

The U-tube procedure, as I have described it here today, was developed as a result of a problem in a patient in 1968, and used in two patients in 1969. In addition, Praderi and Uraguay described a similar technique in 1971.

(Slide) I want to update the published results from Groote Schuur Hospital, Cape Town. We had 26 cases of bile duct junction carcinoma between 1961 and 1972. The last 15 of these have been followed up to the present time. You will see that ten of these 15 patients survived for longer than one year. Two of them are alive and well at 6½ years, having had the U-tube procedure, together with 6000 rads of radiotherapy to the localized area of the tumor.

Four patients had radiotherapy and the U-tube procedure and a total of eight of this group had the U-tube procedure. We subsequently had an inexplicable gap of three years without any patients, but in recent patients we have used a combination of the U-tube and radiotherapy to the localized area. With this type of long-term survival, one just begins to wonder whether we aren't perhaps approaching cure by a very simple technique.

DR. WILLIAM P. LONGMIRE (Los Angeles, California): I would first like to compliment Drs. Cameron, Gayler, and Zuidema for the excellence of their presentation. They, more than anyone in this country, have emphasized the technique of transhepatic intubation in the management of strictures of the common bile duct, and all of us are indebted to Dr. Terblanche for clarifying the use of this transhepatic tube in malignant strictures.

I wish to speak primarily about the benign strictures.

(Slide) The techniques that have to be employed in the repair will vary depending upon the location of injury. In cases where there is a significant segment of dilated common bile duct, such as that seen in this slide, a mucosa-to-mucosa anastomosis with a T-tube stent, generally for one to three months, will suffice.

On the other hand, when the stricture lies high in the hepatic duct, as is so often the case, the mucosa of the intestine is frequently just approximated to the orifices of the ducts. In this circumstance, longterm stenting, as advocated by the authors, is certainly essential. Dr. Cameron indicated that in their series most of the repairs were of this variety. Many of these injuries occur when there is a confusing anamolous condition of the extrahepatic ducts, that leads the surgeon not only to put a clip across the duct or to traumatize it, but to actually excise a large segment of the extrahepatic system.

The principle of longterm stenting in difficult biliary anastomosis (and here I, too would like to digress a moment to mention some historical aspects, like those Dr. Terblanche has brought before us) was really first illuminated by Magoon and Claggett in 1958. They reported 12 cases from the Mayo Clinic in which Vitallium tubes had been inserted to stent a biliary-enteric anastomosis and had been in place for periods lasting from one to eight years. These authors described how in many cases these tubes were simply placed up into the openings in the liver, with the jejunum approximated to the hilus about the tubes, and thus there was really no true biliary anastomosis.

However, when these tubes became occluded and were removed at some point from one to eight years after the original operation, they unexpectedly found a well formed anastomosis, lined with a normal-appearing mucosa. These observations suggested that such repairs might be considered as a two stage operation, first inserting a stent and then, when the stent became occluded, removing it at a second operation. They also demonstrated for the first time the value of longterm stenting.

I was somewhat surprised to discover, as Dr. Terblanche has mentioned, that Görtze probably first described the use of the transhepatic tube for bile duct stenosis in 1951. In 1937, a surgeon on the West Coast by the name of Hoag sutured the redundant gastric mucosa and submucosa, and in 1948 Cole sutured the jejunal mucosa and submucosa to the hilus of the liver over a stent.

(Slide) Experimentally, biliary diversion of bile into a Roux-en-Y jejunal limb is an ulcerogenic operation, as a number of investigators (including ourselves) have demonstrated. Here you can see in the dog's jejunum multiple ulcers that have developed after Roux-en-Y bile diversion. Acid production in a Heidenhain pouch may be increased by as much as 300% following the diversion of bile into a jejunal limb. There is, however, a considerable individual variation of acid increase in such animals, depending upon their normal, pre-experimental acid output.

We have found that in some of our patients with Roux-en-Y bile diversion, acid production has been stimulated. Because of our concern about the ulcerogenic potential of Roux-en-Y diversion, we have utilized a jejunal interposition type of operation.

(Slide) In our experiments with dogs that have responded with an elevated acid output to Roux-en-Y jejunal diversion of bile, we have found that division of the limb and insertion of the distal end of the jejunum into the duodenum cause the acid secretion to return to normal. Bile that returns through such an interposed jejunal segment to the duodenum will protect the patient against a potentially ulcerogenic operation, and at the same time it will prevent the reflux of duodenal contents up into the biliary system.

I have one final comment about bile duct reconstitution. We have two patients in our series in whom it is possible that the bile duct has reformed. In one, the original surgeon had stated that after inadvertently exising a large segment of the common duct, he had inserted one end of a T-tube into the proximal segment of duct and the other end into the distal portion of the duct. We left that T-tube in place for a period of three years, and when we reoperated on the patient to remove the tube, we unexpectedly discovered that the bile duct appeared essentially normal. The duct wall looked normal and it was lined with normal-appearing mucosa. Since removal of the T-tube, the reconstituted common bile duct has functioned satisfactorily for almost two years.

We have one other patient in our series who has a similar history and a third patient who is now under observation for a bile duct avulsion done a few months ago. Although such reconstitution has previously been reported both clinically and experimentally, it has never received serious consideration. I certainly would not advocate this procedure for regular use. In cases like the three we have described, where there was a traumatic avulsion or destruction, a T-tube has been utilized to bridge a duct defect at the time of the original operation as a life saving procedure.

I would like to compliment the authors once again for the excellence of their results and for the techniques they have advanced in this country.

DR. THOMAS TAYLOR WHITE (Seattle, Washington): We have had experience with 14 patients to date in which U-tubes have been placed to palliate carcinoma of the upper bile ducts or metastatic tumors to this area. We differ from Dr. Terblanche's approach in that we bring a Roux-en-Y loop up to this area, having attempted to resect the tumor first. While we have not used the Argyle catheter as he described, we have had the difficulty which he described where the Silastic tube has become compressed and is difficult to change.

The basic question which I would like to ask about the instrumentation which has been used in Baltimore is whether or not this is a special, different kind of Dow-Corning Silastic tube. What we have been using is the 6 mm Silastic tubing which is used for hemodialysis, in which we punch several holes. Are the tubes used at Hopkins prepunched at the factory? Is there some reason why they can get the tubing in and out more easily than the rest of us?

We have had some difficulty with both changing the U-tube and attempting to place it by percutaneous route preoperatively as a method of reducing jaundice. Stig Bengmark told me yesterday that virtually all of the patients undergoing operations for obstructive jaundice in Lund have percutaneous tubes placed into the liver several weeks preoperatively in an attempt to repair a stricture or treat a carcinoma, after which the tubing is pushed through the narrowed area. He says that they have very little technical difficulty, but emphasizes that they take great care with sterile technique.

We have drained ten patients by a similar percutaneous approach.

(Slide) Here is a percutaneously placed catheter which has passed all the way into the duodenum. This was subsequently pulled back and replaced with a Silastic tube. We put a large ureteral catheter on the inside to give it stiffness before we finally got it down into the appropriate position.

(Slide) I would also like to show an instrument we have used in placing the U-tubes which is basically a 3 mm Bake's dilator which has a hole drilled in the end. You can suture the Silastic catheter to it, or tie the Silastic catheter around it. This makes passage of the tube much simpler for us in any case than trying to put Randall stone forceps up through the liver.

Last, I'd like to ask Dr. Cameron and Dr. Zuidema what they feel the advantage is of a single transhepatic tube, as opposed to a U-tube.

DR. THOMAS J. WHELAN (Honolulu, Hawaii): I want to congratulate Drs. Cameron, Gaylor, and Zuidema on their paper, and to thank them for forwarding their paper to me for study early enough to be able to do so.

Their results with benign stricture, as has already been pointed out, are excellent. I have only two questions about this aspect of the paper. First, apparently, in performing their transhepatic stenting procedure where mucosa-to-mucosa approximation is not possible, they do not try to produce a mucosa-lined stent from the jejunum, as Sir Rodney Smith has suggested. I should think that they must feel that this maneuver is not necessary in order to prevent restricturing. I wish they would clarify this point for me.

Second, is there a comment in clarification of the increased incidence of seven benign strictures in the last year, whereas in the previous nine years there were only 18 cases? I presume that the people in the referring community realized that they have somebody who will take care of these difficult cases.

Most of my comments are confined, therefore, to the malignant strictures. We have recently reported 57 cases of bile duct cancer from Hawaii, of which 25 occurred in the common hepatic duct and its confluence. Fifty-eight per cent of our patients were Japanese. Although the population of Japanese to Caucasian in Hawaii is 1:1, bile duct cancer is 6:1 Japanese to Caucasian. The average survival of patients with lesions in this portion of the duct was eight months in our series. In only two of the 25 cases was resection and hepaticojejunostomy possible.

Since the series was concluded in 1975, we have placed three transhepatic U-tube Silastic stents with hepaticojejunostomy, and two of these patients are still alive without jaundice at one and a half to two years. There seems little choice, in our mind, between the transhepatic tube, as described by the authors, and the U-tube, either of which traverses and splints the stricture, allows drainage from the liver to the gastrointestinal tract, and can be changed, when occluded or partially occluded, without resorting to reoperation.

A U-tube additionally, however, can be cleaned out by advancing first one end of the tube to the skin, then the other, so as to expose the holes and allow disobliteration of these holes of bile sludge. This is an office procedure. Cholangitis has not been produced by this procedure in a limited experience. The tube is cleansed with Betadine prior to pulling it back into place.

One late complication we saw with the U-tube was a subphrenic abscess which occurred one year postoperatively as a complication of a rupturing of the tract along the U-tube.

I'm encouraged by the suggestion that radiation therapy may prolong survival in these patients. We certainly are in need of adjunctive measures in management of these discouraging lesions, for which resection has little to offer in tumor control.

Dr. John William Braasch (Boston, Massachusetts): To one who believes that the soul resides in the liver, the idea of skewering the liver with a tube leaves me a little queasy sometimes. However, I would agree that under certain circumstances this method of stenting anastomoses is preferable, especially in cases with very high lesions.

I do have a few reservations in my own mind, perhaps, about what this large bore tube might do to some of the segmental ducts in the liver. We have seen segmental ductal obstruction cause problems, but apparently in this series of cases none were seen.

I would raise one small voice of caution in evaluating results in stricture repair until at least three years have gone by after stents have been removed. In a study about 15 years ago of some of our longterm followups, we found that three years seemed to be about the magic followup time.

I too came prepared with a history of transhepatic stents, and I find I have been outgunned by at least 20 years by these bibliophiles. I would like to point out one thing which has been omitted, a very nice study of Grindly's, reported in 1953, in which he looked into this matter of transhepatic stents in dogs. In the following year, 1954, occurred the first utilization of this technique in the United States in a stricture case by Clagett. I was a witness to the procedure on one end of a retractor.

Dr. Andre Van Rij: I enjoyed this paper a great deal and am very impressed by the results. Dr. Walter J. Pories and I have also found this procedure particularly useful in malignant biliary stricture, particularly at the bifurcation of the common hepatic duct.

However, we have recently observed an interesting and unfortunate complication, which necessitated premature removal of the stent. This occurred in a 65-year-old man who had a malignant obstruction of the bifurcation which was associated with histological changes in the liver of acute cholangitis.

•He was treated with a stent, but despite good drainage across the stent, the bilirubin would not fall below 14 mg%. He then went on and developed a persistent high fever, and *E. coli* was cultured from the bile. Intensive antibiotic therapy, which had been commenced prior to surgery, was continued, and subsequently we grew from the bile both Serratia and Enterococci.

Continuing with the antibiotic therapy, after 18 days, his clinical course continued to go downhill, and at this stage Candida was grown from the bile, and 10^4/ml budding forms were seen. In addition a positive serum serology for Candida was observed. Liver biopsy at that time showed a persistent acute cholangitis, but there were no mycelial forms.

It was only with the removal of the stent that his clinical course improved, and then it did so very markedly and promptly. His temperature fell, his bilirubin returned to normal, and he was discharged one week following removal of the stent.

At present, two months later, he remains unobstructed with a normal bilirubin.

The reason for bringing this complication to your attention is that, interestingly, Candida is uncommonly reported to appear in the biliary tree. Superinfection with Candida, however, is more common in debilitated patients and particularly with intensive antibiotic therapy. The presence of Candida has also been reported in association with central venous catheters and with prosthetic heart valves.

Here we have a group of patients undergoing the procedure described by Dr. Cameron who would also appear to be at a greater risk of such infections with the introduction of a foreign body. I would like to ask Dr. Cameron whether in his patients, bacteria were cultured from the bile when placing the stent and whether this had any effect on the morbidity associated with this procedure.

Dr. John L. Cameron (Closing discussion): I think the number of individuals discussing this paper attests to the difficulties of management that still remain with biliary strictures.

In regard to the U-tube versus the straight tube with the distal end left in the Roux-en-Y loop, I think that's basically a matter of personal preference. However, I think patients prefer to have as few tube ends on their abdominal wall as possible. Particularly in malignant strictures, we feel both the right and the left duct should be intubated and that leaves you with four ends out on the abdominal wall if each is a U-tube. The only advantage of the U-tube that I know of is that it can be easily changed; but the straight tubes can be just as easily changed with a stylet with only one end out. Certainly a U-tube, I think, is just as satisfactory as a single tube.

In terms of the mucosal graft technique, we have not used that. Sir Rodney Smith has published his results, and using the mucosal graft technique and leaving a latex stent in for four months, he has good results in somewhere between 65 and 70% of his patients. We really think that the important aspects of our repair in benign strictures are the fact that a Silastic stent of large bore is used, and that it is left in for a period of 12 months. We have had virtually no failures with this technique. These tubes are produced commercially by Dow Corning. They are very thick walled and are noncompressible by tumor or any other natural means. They are much thicker than the tube shown in the picture by Dr. White, and I think it's really quite impossible to have these tubes compressed.

We have used percutaneous intrabiliary placement of a smaller, 3 mm catheter fairly routinely in these patients prior to surgery and used that catheter placement to withdraw our transhepatic stent during the operative procedure.

In answer to Dr. Braasch's question, the cholangiograms obtained through the transhepatic stents show all of the segmental branches beautifully. The multiple side holes, I think, avoid obstruction by these large-bore stents.

One Per Cent Incidence of Recurrent Gallstones Six to Eight Years After Manometric Cholangiography

THOMAS TAYLOR WHITE, M.D., JAMES BORDLEY IV, M.D.*

The national incidence of retained and recurrent common duct stones is between 2 and 7%. A prospective comparison of operative common duct pressure flow rates as opposed to operative cholangiography was commenced in 1968 to assay another diagnostic technique to assist in the reduction of this rather high incidence of recurrence. We are now reporting the 6–8 year follow-up data on the first 200 patients, 190 (95%) of whom were reevaluated in 1977. In our inital reports we were surprised to find that our accuracy with flow and pressure studies was 93%, not significantly different from that found with operative cholangiography (92%). The measurements of flow, resting pressure, and opening pressure in the patients with stones or strictures at the lower end of the bile duct were each significantly different from those found in normal ducts ($p < 0.001$). We considered normal flow to be 10 ml/min saline at 30 cm of pressure and normal intrabiliary pressure to be less than 16 cm of saline was measured through the cystic duct. To date only one individual has had to undergo reoperation for stones and another for recurrent biliary obstruction. A third individual is suspected of, but not proven, to have a retained stone. No patient who had a normal operative cholangiogram, flow and pressure studies, has had a late recurrence of stones. We have presented the specifications of a new catheter for performing flow and pressure x-ray studies, which we feel may be used to primarily evaluate the distal duct with greater accuracy and clarity. We think that this inexpensive but reliable method has an important place in biliary surgery, particularly where operative cholangiography may not be available, or, for one reason or another, is not reliable.

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SYMPTOMS ATTRIBUTABLE to residual gallstones and obstruction of the lower end of the bile duct are reported to occur in from two to 7% of patients undergoing cholecystectomy with or without common bile exploration.[2,8,16,20,24,26] We feel that any method which will find a greater proportion of the pathology at the primary procedure would be welcome. Furthermore, the number of fruitless choledochostomies with its associated increased morbidity and morality should be further reduced.

Prior to the advent of operative cholangiography the only indications of stones or other abnormality of the distal bile duct were: a history of jaundice, acute pancreatitis, a raised bilirubin, alkaline phosphatase, or amylase, fever and chills suggesting cholangitis, or stones which were palpable in the common bile duct at the time of surgery. Further, most surgeons have considered an abnormally large common or cystic duct, or one with multiple small stones, to be an indication for a common duct exploration.

In 1947, 45% of all patients undergoing cholecystectomy at the Swedish Hospital in Seattle had common bile duct explorations. This figure decreased to 37.2% of 1,590 cases in the years 1948–1957, with 27.8% of those patients explored having common bile duct stones. The rate of exploration dropped again to 24.5% of the 2,235 cases done between 1958 and 1967, with 40.3% of the ducts explored containing stones. It was felt that the main reason for the reduction in the rate of exploration was the advent of operative cholangiography at this hospital in 1952[11]. In a study of 193 patients left with residual common duct stones, we noted that only 3.6% of the stones found in the common bile at the primary operation were palpable; a common bile duct over 10mm in diameter was found in only 20%; jaundice in 17%; pancreatitis in 7%; cholangitis in 3%; and cystic duct stones in 2.6%. It also has become apparent to us that many stones 3mm or less in diameter were not being routinely seen in operative cholangiograms and that obstruction of the lower bile duct due to fibrosis, pancreatitis, or carcinoma could not always be identified in routine cholangiograms.

It was for this reason that we became interested in manometric operative cholangiography as introduced by Caroli in 1946[5] as an additional means of evaluating the distal common bile duct and the sphincter of Oddi. This technique has been used by many surgeons with success, especially in Europe and South Amer-

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•Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

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ica,[1,3–5,16,17,27] but it has not been popular in any English speaking countries.[6,7,9,17–19,21,22] The technique has been thought to be extremely helpful, especially in the detection of small stones in the distal bile duct and stenosis of the sphincter of Oddi.

A prospective study of operative manometric cholangiography was begun in Seattle in 1968 with the idea of assessing its value in reducing both the incidence of residual common bile duct pathology and the number of unnecessary bile duct explorations. The initial results of this study were previously reported.[10,13,25] A seven to nine year follow-up is now available on the first 200 cases studied, and the results will be re-examined in the light of a long-term follow-up.

Materials and Methods

Manometry, cholangiograms and flow studies were performed on 199 patients undergoing 200 biliary operations in eight Seattle hospitals between 1968 and 1971. Most of the operative procedures were carried out at the University of Washington and Swedish Hospitals. There were 180 primary biliary procedures and 20 secondary procedures carried out. There was no special preoperative aside from a precaution insuring that the patient had not received any drug which would produce spasm of the sphincter (morphine, dilaudad, demerol (meperidine hydrochloride), codeine, *etc.*) for at least 90 minutes prior to manometry, by which time any direct effects of these drugs on the sphincter would have worn off. Most patients received atropine with premedication. In the first 99 patients the Fauré modification of the Caroli apparatus was used. The reservoir and tubing were filled with 15% solution of Hypaque® (sodium diatrizoate) taking care to exclude air bubbles. The cystic duct was cannulated with a Champeau metal cannula. The zero marked on the manometer scale was adjusted to the level of the common bile duct using 50 cm long metal rod which was attached to its spirit level. At the start of the observation the reservoir was held at the zero mark and clamps including the tubing were opened. The reservoir was then raised slowly at 1–2 cm intervals up the scale until continuous bubbling was seen at a steady pressure. A few bubbles went through the apparatus each time the reservoir was raised because of the rise in fluid level within the manometer. The lowest pressure at which continuous bubbling occured was called the opening pressure (OP) and it indicated the point at which the resistance of the sphincter had been barely exceeded. The first x-ray was taken at this point. The reservoir was then moved up to 50 cm and another cholangiogram x-ray taken promptly. The reservoir was then clamped off from the system and the radiopaque media was allowed to fall to a steady pressure which we called the resting pressure (RP) usually 2–3 cm below the opening pressure. We and the nurses found this apparatus somewhat complicated.

Flow Studies

For this reason a modification of the apparatus described by Besançon[3] and Casal[4] was used in a second group of 101 patients. Because of its simplicity and the good results we have continued with an apparatus which consists of a barrel of a 50 ml glass syringe to which a gas-sterilized extension tubing was attached by an intervening stop-cock. The tubing was in turn connected to a plastic cannula made by the Cardiovascular and Special Instrument Division of the Becton-Dickinson Co. (SH 2311). This cannula is approximately 1 mm in internal diameter, and has a bulb about 15 mm from the tip, and two side-holes in addition to the distal opening. This is all gas-sterilized before the operation. A rubber stopper with a glass tube is placed in the barrel of a 50 ml syringe so that the glass tube is opposite the 10 ml mark (Figs. 1 and 2).

The cystic duct was cannulated in such a way that the tip of the cannula rested in the common bile duct. The lower end of the 30 cm steel ruler was placed at the level of the common bile duct with the lower end of the glass tube in the syringe held adjacent to the top of the ruler (Fig. 4). The stop-cock was then opened and saline was allowed to fill the bile duct until the rate of the bubbling became constant. The quantity of saline flowing out of the syringe in one minute was then measured. The syringe was then disconnected and another syringe

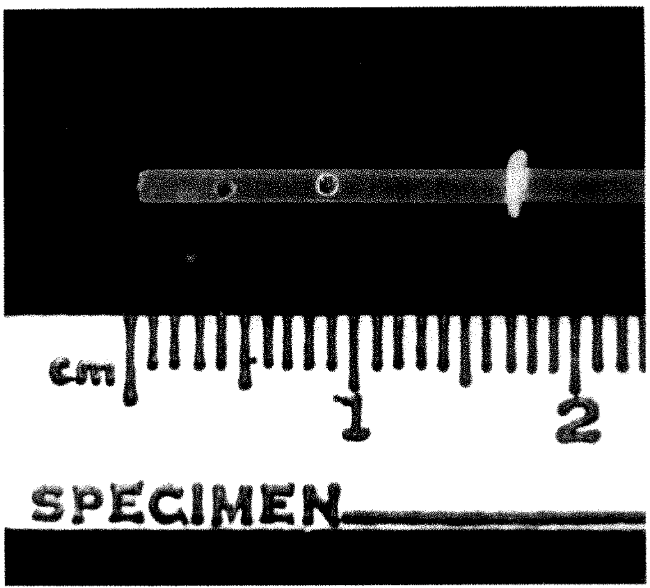

FIG. 1. The tip of the cannula used in the last 70 cases showing the side holes and the bulb used to tie it in after insertion into the cystic duct.

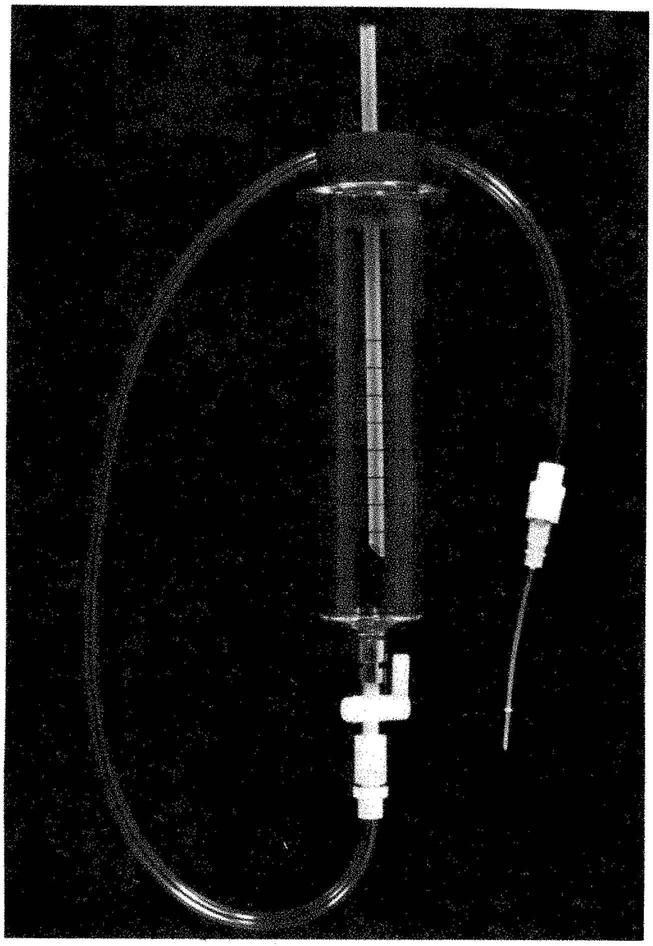

FIG. 2. The entire apparatus used now, including cannula, clear connecting tube, 50 ml syringe barrel, and contained constant pressure tube.

containing 15% Hypaque (sodium diatrizoate) was attached and cholangiograms were obtained. After the x-rays were completed the syringe was disconnected and the fluid in the tubing allowed to run into the common bile duct until it stopped dropping. The height of the fluid column above the common duct was measured with the ruler. This reading represented the resting pressure of the common bile duct.

Follow-up data was obtained by direct contact with the patient or his physician.

Results

The operative cholangiograms were interpreted at the time of surgery as positive (showing pathology), negative (no pathology), or technical failures. The results are summarized in Table 1. The technical failures were chiefly due to problems with the cannula (Table 4). These fell from seven out of the first 50, to six each in the second and third 50 patients studied, and to one in the last 50, during which time we used only the new plastic cannula.

The results of manometry were interpreted as positive, negative, uninterpretable, or technical failures. On the basis of our prior studies and those of others, the highest normal opening and resting pressures were considered to be 15–16 cm of water.[6,7,9,14,18,19] In our series, any pressure 16 cm or greater was considered to be abnormal. Any flow rate greater than 10 ml/min at 30 cm of pressure was considered to be normal (extrapolating from the work of von Brücke[23] and Daniel.[6] A combination of the opening and resting pressures was used to determine normality in the first group, and in the latter group flow and resting pressure were used. If the two values disagreed, the combined manometry was considered to be equivocal.

We have divided the 200 studies into six groups according to the x-ray and manometry results as illustrated in Table 6 (Fig. 3). Both manometry and x-ray were successful in 158 patients (79%). Groups I, II, and III are included in this group of patients. Group I consisted of 121 patients in which both manometry and x-ray

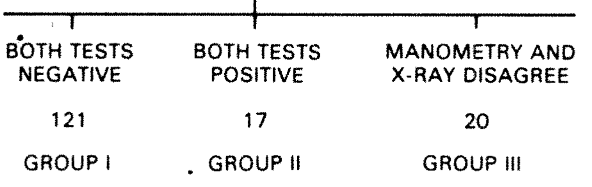

FIG. 3.

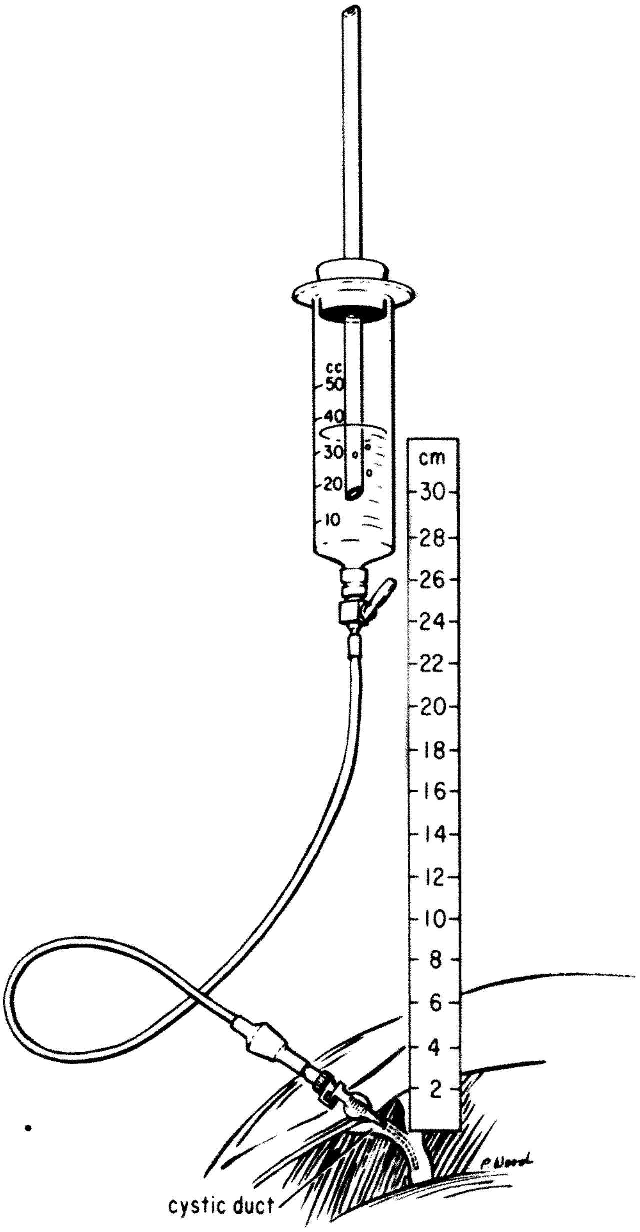

FIG. 4. Schematic drawing of the apparatus connected with the patient.

TABLE 1. *Immediate Results of Flow and Pressure Studies*

	Number of Attempts	Positive	Negative	Uninterpretable	Technical Failures
Cholangiography	200	30	153	—	17 (8.5%)
Resting pressure only	200	40	139	—	21 (10.5%)
Flow only	101	13	79	—	9 (4.5%)
Flow and pressure	101	13	76	3	9 (4.5%)

indicated no pathology. In this group were 15 common bile duct explorations where no significant pathology was found. The reasons for exploration are shown in Table 2. Sphincteroplasties were performed in the 8 patients with pancreatitis in the hope that decompression of the pancreatic duct would prevent further attacks. The other explorations were because of multiple small gallbladder stones, cystic duct remnant, pain and fever, an enlarged common bile duct, and a technical error. 106 further patients in Group I did not have a common bile duct exploration. In 96 of these the operative diagnosis was cholecysterolosis, cholecystitis, or cholelithiasis with no other problem. Three patients had pancreatitis without gallstones, two had a cystic duct or gallbladder remnant, and five had a cholecystectomy performed where no biliary or pancreatic pathology was found. Most patients have done well with no late reoperations (Table 3). There have been two instances of recurrent pancreatitis, both in patients who had pancreatitis without gallstone disease at the time of the original operation.

Group II included 17 cases in which both x-ray and manometry were positive. Common duct explorations were performed in all of these patients and pathology was found in every instance. Common bile duct stones were found in 11 instances. Four patients had pancreatitis with such severe stenosis of the distal duct that a choledochoenterostomy was required. One patient had common bile duct obstruction secondary to tumor. The last patient had stenosis of the sphincter of Oddi. Again there were no late reoperations in the patients contacted (Table 3). Those still alive have no evidence of significant biliary pathology.

Group III includes 20 cases where the x-ray and manometric studies disagreed. In 14 instances, the manometry was positive and x-rays were interpreted as negative. Ten of the 14 ducts were explored with five instances of small common bile duct stones, three of stenosis of the sphincter, and one of sclerosing cholangitis originally reported as carcinoma. One explored duct and four unexplored ducts had no demonstrable pathology at the time of the operative procedure. None of these five have had any problems since the time of surgery. Thus manometry was correct in nine of these 14 patients and x-rays in five out of 14.

TABLE 2. *Reasons for CBD Exploration in Group I*

Reason	Number
Pancreatitis	8
Multiple small stones	2
Technical error	2
Cystic duct remnant	1
Pain and fever	1
Enlarged CBD	1

TABLE 3. *Combined Follow-up Chart*

Groups	I	II	III	IV	V	VI	Totals
Asymptomatic	79	6	12	20	2	6	125
Vague abdominal problems	25	1	3		2	3	34
Recurrent pancreatitis	2					1	3
Biliary reoperation			1	1			2
Suspected recurrence			1				1
Dead of other causes	10	7	3	3	3	2	25
Lost	5	3	0	1		1	10
Totals	121	17	20	25	6	11	200

Six of the Group III patients had positive x-ray findings and negative manometry. All six ducts were explored and stones were found in the common or hepatic duct in four instances. X-rays were correct in four of these six patients and manometry in two of them. There were two negative explorations, later attributed to air bubbles. Late follow-up of the patients in Group III (Table 3) indicated that there were two patients with recurrent problems. The first was a 58-year-old man who had negative x-rays with positive manometry. He had a hard, fibrotic pancreas, and had previously undergone cholecystojejunostomy for suspected carcinoma. Cholecystectomy and sphincteroplasty were performed. A biopsy of his papilla revealed papillitis and fibrosis. Postoperatively he continued to have problems with jaundice and pancreatitis with the result that he had a reoperation one and one-half years later with a second manometic cholangiogram. Choledochoduodenostomy was done at that time. He has been asymptomatic in the ensuing nine years. The second, a 67-year-old man had normal manometry and abnormal x-rays. Cholecystectomy and common duct exploration were performed at which time a single stone was found in the common bile duct. A five mm dilator passed easily through the sphincter. The patient did well initially but recently has had several episodes of colicky abdominal pain with elevations of alkaline phosphatase and bilirubin. While an intravenous cholangiogram showed a 15 mm duct with no stones, it is possible that he has recurrent stones. He is not interested in further surgery.

Group IV includes 25 cases in whom only x-ray studies were successful and unequivocal. There were seven positive cholangiograms and all seven had common bile duct explorations. One exploration was negative but pathology was found in the other six: three had stones, two stenosis, and one a tumor. Two ducts with normal cholangiograms were explored with no pathology being found. The 16 patients with unexplored ducts showed no common duct pathology at surgery and have had no biliary problems since then. One patient in this group had a second biliary procedure. This 16-year-old girl initially had a cholecystectomy and sphincteroplasty because of common duct stones and recurrent acute pancreatitis on this basis. It is now felt that she had congenital pancreatitis. She developed recurrent bile duct obstruction which required a reoperation for removal of further bile duct stones, and a choledochoduodenostomy.

Group V contains six patients in whom manometry was successful and x-rays were not. Two of the three who had positive manometry had their ducts explored. One had stenosis and inflammation of the sphincter. X-ray was not attempted in the second with a pancreatic tumor. The other four ducts appeared normal at the time of surgery and these four patients have had no biliary problems during the follow-up (Table 3).

Group VI contains 11 patients in whom neither study was possible. One common bile exploration in this group was done in a patient with pancreatitis and no gallstone disease. A sphincteroplasty was performed on the pancreatic duct. This patient has had recurrent pancreatitis but there have been no other significant late problems (Table 3).

The combined follow-up data for all patients is shown in the right hand column of Table 3. Good follow-up information was obtained in 95% of the patients after seven to nine years.

Discussion

Manometric cholangiography has been easy to perform. It adds less than five minutes to the normal operative procedure. The flow and pressure measurements used in the last 101 patients were considerably easier to perform than measurements carried out earlier with a Caroli apparatus. We were upset by the number of technical failures (Table 4) and inconclusive studies in the earlier patients. Still there was only one technical failure in the last 50 patients in the series as opposed to seven in the first 50, and six each in the second and third 50. We failed to take cholangiograms in 17 out of the 200 patients (8.5%). The new plastic cholangiography catheter used in the last 80 patients has been much easier to use than the metal Champeau catheter which we used in the earlier cases.

The overall accuracy of x-ray manometry as determined from operative findings and follow-up data has been summarized in Table 5. The results from pressure

TABLE 4. *Reasons for Technical Failure: 20 Patients*

Reason	Number
Cannula too large	10
Cannula twisted	7
Catheter too small	1
Leak around catheter	1
Unknown	1

TABLE 5. *Accuracy of Studies*

	Uninter- pretable	False Nega- tive	False Posi- tive	Accuracy
Clinical signs only	0	18/200	22/200	40/200 (80%)
Cholangiography	0	3/183	9/183	12/183 (93%)
Resting pressure only	0	11/179	7/179	18/179 (90%)
Flow only	0	5/91	3/91	8/91 (91%)
Flow and pressure	3	5/89	2/89	7/89 (92%)
Manometry and chol- angiograms agree	0	0/138	0/138	0/138 (100%)

TABLE 6. *Manometry and X-ray Attempted: 200 Patients*

Group	# Cases
Manometry and X-ray Successful and Unequivocal	
I. Both Tests Negative	121
II. Both Tests Positive	17
III. Manometry and X-ray Disagree	20
IV. X-Ray Only Successful	25
V. Manometry Only Successful	6
VI. No Studies Successful	11
Total	200

alone, flow alone, flow and pressure, and x-ray alone, vary from between 90–93% accuracy. The greatest accuracy occurred when manometry and cholangiograms agreed, as in Groups I and II, where the accuracy was 100%.

We found 11 cases of distal common bile duct pathology (nine from Group III and two from Group V) which were not revealed by x-ray. One of these patients had a tumor which had not been recognized before the test was performed. The other ten had common bile duct disease which was not obvious, which was not noted on x-ray, and which probably would have gone undetected if manometry had not been performed. Five of these patients had small stones, four had stenosis of the papilla, and one had a sclerosing cholangitis. On the other hand the cholangiograms revealed pathology in four cases where manometry was negative and six instances where manometry was unsuccessful. For this reason we recommend that both modalities be used.

We were particularly interested to note that none of the patients in whom both manometry and x-ray were negative (Group I) had any bile duct pathology at surgery or during the late follow-up period. The 106 patients in this group who did not have common bile duct explorations have had no evidence of recurrent disease of the biliary tree.

Our results indicate therefore that radiologic and manometric studies of the bile duct are complimentary. Each has advantages. Manometry is particularly useful in revealing small stones and diseases involving the papilla with almost the same accuracy as cholangiography. Cholangiography is more useful in revealing stones well away from the sphincter of Oddi. The accuracy of manometry and cholangiography is greater than with either test by itself.

One upsetting aspect of this study was that 60 (30%) of the 200 patients had a common bile duct exploration, 21 (35%) being explored unnecessarily. 15 Group I tests where both tests were negative were unnecessarily explored. We felt that unnecessary exploration might have been avoided if more faith had been placed in the flow and pressure results.

We are, however, impressed that only three out of the 200 patients in this study have any evidence of recurrent biliary problems. Only two of the patients have been reoperated to date. This results in less than half the number of reoperations of any other reported series.

Conclusions

We feel that our studies have shown that manometric cholangiography, particularly flow and pressure studies, are easy to perform and useful in making the diagnosis of pathology of the distal common bile duct. We currently feel that flow and pressure studies should be carried out as a routine in all patients undergoing cholecystectomies as well as operative cholangiography. If both bests are positive, the common bile duct should be explored. If one test is positive, the duct should be explored unless there is an obvious technical error. If neither test is positive we hesitate to explore the common bile duct even in the face of traditional indications for exploration. A flow and pressure study by itself has an accuracy so close to that of operative cholangiography, that this approach might be used as a screening test in instances where cholangiography is not readily available.

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DISCUSSION

DR. FRANK G. MOODY (Salt Lake City, Utah): Dr. White and his colleagues in Seattle have done us a service by continuing to pursue their interest in radiomanometry. This is a technique that has been used for about 30 years in Europe, and apparently with good success. In America there has been sporadic application, and, actually, great reluctance to use it; and I guess that relates, possibly, to its lack of specificity and reproducibility.

For example, if both tests are consistent and positive, then you'll always find pathology in the duct. Therefore, that would mean to me that the cholangiography would be equally good, and I guess Dr. White would agree with that, because he stated that the manometry could be used in the place of cholangiography in this situation.

Now, if the manometry is positive and the cholangiography is negative for identifying pathology, then you have a 35% false-positive rate, which is extremely high for any type of diagnostic procedure that one can apply clinically.

We have taken this problem to the laboratory, and we have studied rhesus monkeys in a restraining chair, developing flow/pressure relationships, without any type of medication in these animals, and we've found that on any given day, indeed, we could get reproducible curves, but on other days we couldn't reproduce the same curves.

We became curious about this and decided to test it on the opossum so we could place electrodes into the sphincter and measure the spike potentials. The reason why we used the opossum is that their sphincter of Oddi is outside the duodenum. We chose to study the GI hormones, rather than the neural control of the sphincter, and we found very early that glucagon, cholecystokinin and, to our surprise, pentagastrin caused a marked increase in the spike potentials and a decrease in the rate at which materials could be perfused through the common bile duct in these critters.

I suspect that these hormones, possibly, are playing a role in Dr. White's patients. Now, I realize that they can't be quantitated or measured; but one might be able to overcome this by using some type of a dilatory substance on the papilla, and I wonder if, indeed, you did use amyl nitrite in some of your studies.

In addition, did you also make measurements after you removed the stones, or cut the sphincter?

I hope that Dr. White and his colleagues will continue to try to apply this particular technology. In some way, it's helping them, because a 1% incidence of overlooked stones is really a tremendous accomplishment. I imagine it relates more, however, to their very careful attention to detail in their cholangiography, and in their way that they actually carry out the explorations of the ducts, rather than to the value of this particular test.

DR. GEORGE D. ZUIDEMA (Baltimore, Maryland): I would like to comment on several points which Dr. White's manuscript has raised.

First of all, going back to the presentation which Dr. Egdahl made earlier, we would all agree that it's important to avoid unnecessary common duct explorations. It's been shown to double the mortality and to increase the hospital stay by five days, not to mention the additional discomfort which the patient experiences. Therefore, any test which would improve the accuracy of diagnosis should conceivably be of considerable help.

The basic idea, then, is to improve the accuracy of common duct exploration.

Now, let us take a quick look at the various groups which Dr. White showed us; I'd comment on two of them. First of all, in Group 4, with 25 patients in whom the x-ray examination was successful, there was only one unnecessary common duct exploration. In Group 1, however, with 121 patients, in which both the radiology and the manometry were satisfactory, there were 15 negative common duct explorations.

It seems to me that some of these may have occurred when they were gaining experience with the technique; but at any rate, the unnecessary operations were there.

The technique, it seems to me, has some advantages and some disadvantages. I think that in taking it up we would all probably experience the same kind of learning curve which Dr. White and his colleagues showed, with a relatively high incidence of technical failures early in the experience.

There is a major problem, however, which is hard to get around. If we were to rely on the manometry alone, we would have the problem of detecting intrahepatic stones. For this reason, I feel that it's unlikely that the cholangiography used alone as a screening test would be very helpful, because I think if we were to take one examination, we would probably get more information from a cholangiogram. There might conceivably be an advantage in the obese patient, where we're all familiar with the technical problems associated with cholangiography.

Now, this study is based on a simple hydraulic system, and therefore should lend itself to the construction of a model where one can vary the size of the stones within the model, the rigidity of the duct wall, and so on. I'd like to ask Dr. White if he knows whether it has been studied in this way, so that the laws of hydraulics can be applied.

Finally, if the resting pressure alone would be of any value in a screening fashion, combined with cholangiography, I wonder whether he's had the experience using a readily available central venous pressure catheter, one which would be available in every operating room and could be used without investing in a lot of special equipment.

DR. JOHN WILLIAM BRAASCH (Boston, Massachusetts): Dr. White has the disadvantage in this study of starting with a low recurrent stone rate so any meaningful change in this level by his added technique is difficult to establish.

We have had no experience with manometric cholangiography and have preferred to use the choledochoscope as an adjuvant procedure for examination in large ducts. We feel that this has been helpful in finding the overlooked stone in the proximal system, where most of our recurrent stones have hidden.

We should all realize, of course, that with the advent of postoperative stone manipulation through the T-tube tract, the overlooked stone is no longer the great tragedy that it used to be. Our radiologists are getting quite good as this technique, even extracting stones from the tertiary radicles within the liver. Then, too there is the technique of fiberoptic papillotomy, which I am certain allows many overlooked stones to pass.

DR. THOMAS T. WHITE (Closing discussion): I certainly appreciate the discussion. As far as Dr. Moody's question about dilating substances, we have used amyl nitrite or glucagon to get rid of the abnormalities. Relative to measuring pressure after a common duct exploration, the pressure goes up every time you pass an instrument through the sphincter so that, in most instances, pressure measurements at this point are meaningless unless we do a choledochoduodenostomy or a sphincteroplasty, when it should be normal.

As far as Dr. Zuidema's question about Group I versus Group IV, there is no question that many of the ten surgeons involved in the project did not believe the test in Group I patients at the beginning of the study. Thus, if they thought the bile duct needed to be explored, they went right ahead and did it. It is for this reason that there were 15 negative explorations out of 121. It is certainly true that intrahepatic stones would not be shown by this technique. Owen Daniel has done a series of flow and pressure studies using different sizes of openings at the end of the tubing in an experimental hydraulic system. This shows that an opening of 0.1 mm will allow a flow of 10 ml per minute at 30 cm of water. Professor Von Brücke from Linz, Austria, has done the same thing and drawn the same conclusion. As far as the Intracath or other tubing of this nature, the problem with flow studies using a 5-F children's feeding tube is that you will only get a flow of about 3 ml per minute through the system because of the internal friction. Tubing which is of the same diameter for the whole length has so much friction that it slows the flow even of saline. Flow is slowed even further if radiopaque medium is put into the tubing rather than saline. For this reason we use a small cannula at the end and a large IV tubing above which allows about 40 ml of saline to pass through the system per minute.

Relative to Dr. Braasch's question, I'd like to say that choledochoscopy should be followed by T-tube cholangiograms even if the visual examination appears to be normal, because of the possibility of residual stones out of the field of view. Second, we have had more overlooked stones in patients who had a bile duct 7 mm or less in diameter than with patients with big ducts. In these patients we cannot use a Berhenne directable cannula to remove the stones and have to have a second operative procedure or an endoscopic papillotomy.

Book Reviews

Clinical Gastroenterology, 2nd edition. Howard M. Spiro. 1289 pages. New York, MacMillan. 1977. $45.00.

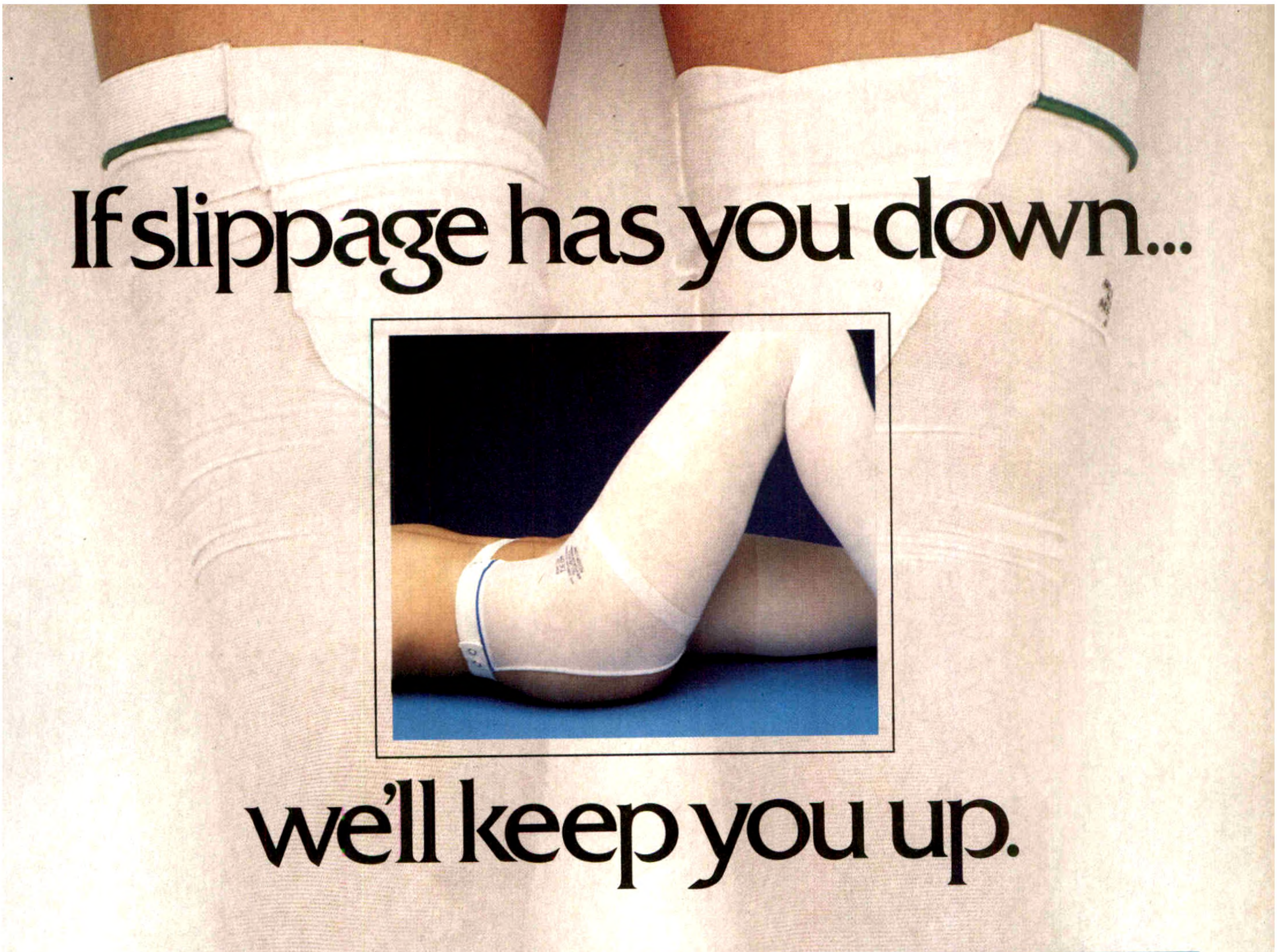
IN 1970, THE FIRST EDITION of Spiro's *Clinical Gastroenterology* was introduced and immediately became one of the most sought after textbooks of gastrointestinal diseases. Dr. Spiro now offers a revised and considerably updated second edition which will undoubtedly prove to be at least as popular as the first. Drawing upon his experience of more than 25 years as a noted gastroenterologist, and upon the information contained in over 3,600 references, Dr. Spiro has again produced an unusually readable and highly relevant reference. Commonly encountered problems which are given special emphasis in this text include structural disorders of the esophagus, inflammatory and neoplastic disorders of the stomach, peptic ulcer disease, structural disorders of the small bowel including malabsorption syndromes and neoplastic diseases, tumors of the lower bowel, pancreatitis and associated disorders, hepatitis, and cirrhosis. A newly organized section on inflammatory bowel disease and its complications is particularly well written and represents one of the finest reviews of these disease processes found in print. Because the topics that receive special emphasis are of frequent concern to the internist, gastroenterologist, and surgeon alike, the textbook is an unusually practical reference source in the clinical setting.

Of particular interest to the surgeon are excellent sections on postgastrectomy syndromes and postcholecystectomy syndromes. These sections represent excellent reviews of these problems, and general surgeons will find them particularly relevant and helpful. A few of Dr. Spiro's comments regarding surgical approaches to diseases of the gastrointestinal tract will probably meet with disagreement on the part of some of his surgical readers, as for example his opinion that surgical correction of reflux gastritis following gastrojejunostomy is futile, or his suggestion that early and continuous bougienage of acute lye burns of the esophagus be performed. Overall, however, indications for operations on the gastrointestinal tract are clearly and rationally established throughout the text.

Beautiful reproductions of radiographs illustrating the disorders covered are found in almost every section of the book and it is apparent that Dr. Spiro credits much of the successful care of gastroenterologic problems to the competence of his radiologic colleagues. It is a little disappointing, however, that there are no reproductions in the textbook of views of the gastrointestinal tract as seen through the fiberoptic endoscope. Although the statement is made throughout this edition that endoscopy has a primary role in the evaluation of many gastrointestinal disorders, it is unfortunate that no illustrations of this now widely used technique are to be found.

Reflecting Dr. Spiro's expertise, approximately 80% of the textbook is devoted to diseases of the alimentary tract and only 20% to primary disorders of the liver. This means that the vast majority of the textbook is extremely relevant to the problems most dealt with by gastrointestinal surgeons. In addition, the strength of this book lies in the scholarly approach to these disorders taken by the author, and his impressive clinical experience in the field. It is an unusually well written and valuable reference for all physicians who treat disorders of the gastrointestinal tract.

DANA K. ANDERSEN, M.D.



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- Side panel and waist belt assure reliable continuous non-slip protection
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Contraindications: Stockings may not be recommended for patients with the following: **1.** Any local leg condition in which stockings would interfere, such as: **a.** dermatitis, **b.** vein ligation (immediate post-operative), **c.** gangrene, **d.** recent skin graft. **2.** Severe arteriosclerosis or other ischemic vascular disease. **3.** Massive edema of legs or pulmonary edema from congestive heart failure. **4.** Extreme deformity of leg. **5.** For thigh length, patients with a circumference greater than 25 in. (63.5cm) at the gluteal furrow. For full-leg (X-S,S,M,L), patients with a circumference of 25 in. (63.5cm) or greater at the gluteal furrow. For full-leg (X-L), patients with a circumference greater than 32 inches (81.3cm) at the gluteal furrow.
Precautions: 1. Proper sizing and application must be assured. **2.** For full-leg style T.E.D. Stockings avoid interference of side panels or waistband with incisions, drainage tubes, catheters or other exterior devices.
Warnings: Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

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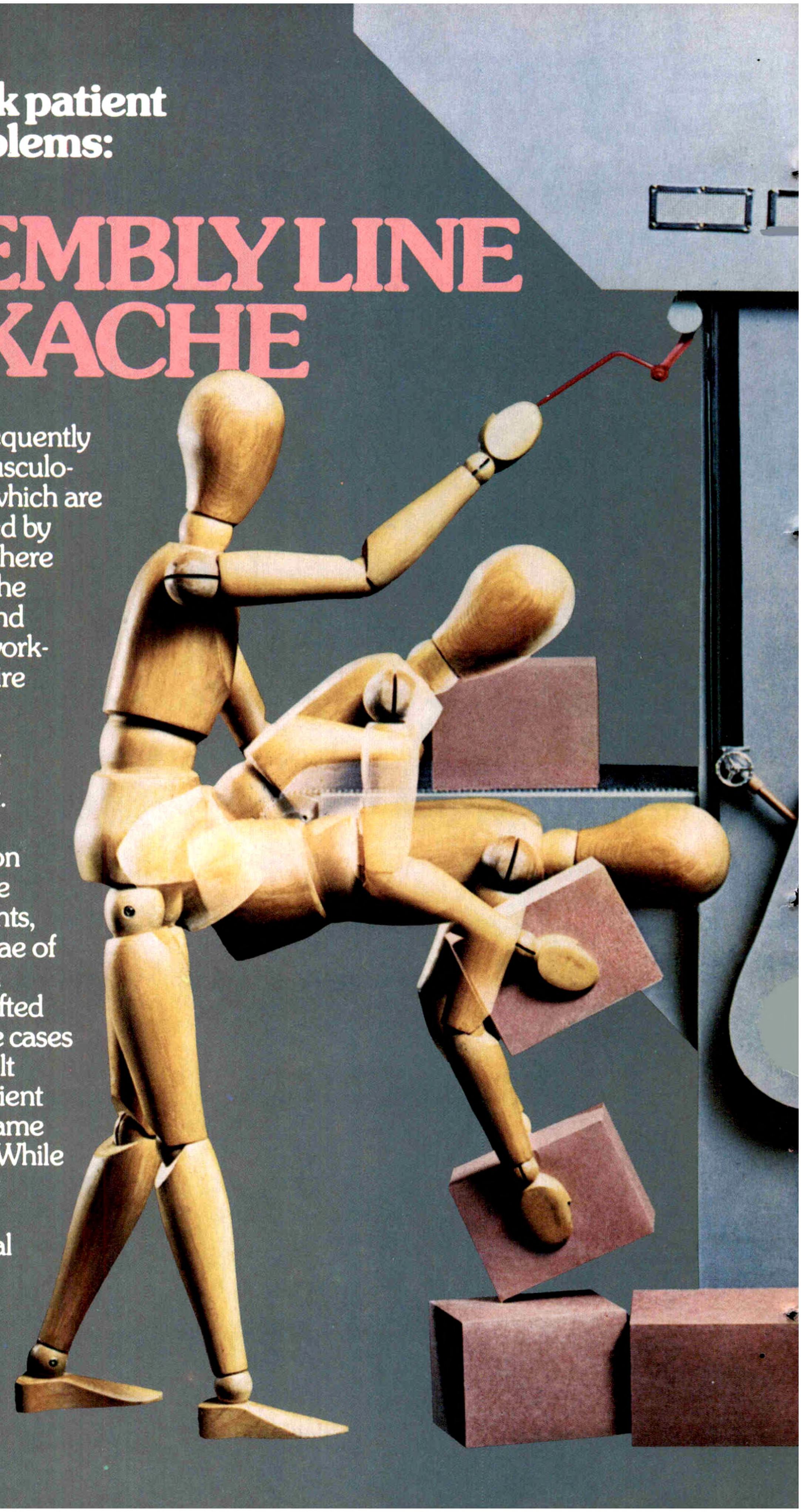
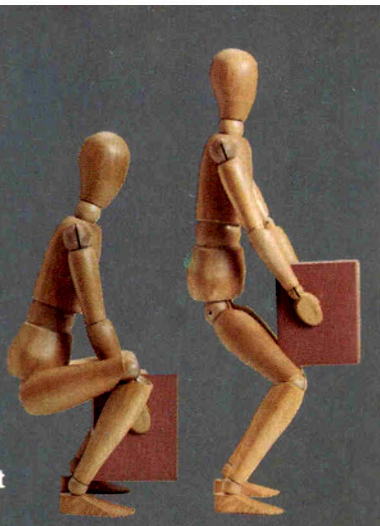
the low-back patient and his problems:

ASSEMBLY LINE BACKACHE

Chances are you frequently see patients with musculoskeletal conditions which are caused or aggravated by assembly line jobs where they must perform the same activity over and over again. Those workers whose jobs require repetitive lifting or bending are most likely to complain of low-back discomfort. Unnatural motions repeated for hours on end can place undue strain on the ligaments, muscles and vertebrae of the lower back, even though the objects lifted are not heavy These cases are especially difficult to manage if the patient must return to the same job after treatment. While he can't avoid lifting altogether, he can benefit from practical instructions on the correct way to lift and suggestions on how to break up his routine.



Lift with the legs, never the back
This rule applies, even when picking up a scrap of paper. The patient should never bend forward or sideways from the waist, or lift from a bending-forward position. He will better understand why it is important to let the legs do the lifting if you explain that those strong bones and powerful muscles can withstand the strain far better than 24 movable vertebrae in a curved line. You may find it helpful to demonstrate the correct way to lift. Squat in front of the object keeping it close to the body. Then slowly rise to a standing position. The patient should never lift with his legs straight.



Advice to all low-back patients
Avoid lifting objects from car trunks, reaching over furniture to open windows, etc. Don't make beds or run the vacuum cleaner when the back is "acting up." If the patient's job requires repetitive lifting or bending, he should follow correct procedures and periodically take a rest to break up his routine. He may be able to perform the work seated or standing with one foot resting on a small stool. Perhaps his employer can find something different for him to do occasionally. If his back continues to bother him, he will probably have to consider getting a different kind of job.

as an adjunct in the relief of discomforts associated with acute, painful musculoskeletal conditions

ROBAXIN®-750

(Methocarbamol, NF)

750 mg capsule-shaped tablets

the Robaxin regimen:

Bed
Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort.

Board
Have patient insert section of ½" or ¾" plywood between mattress and box springs.

Heat
The judicious use of moist heat is often very beneficial.

Robaxin-750 can relieve the discomforts associated with acute musculoskeletal conditions. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

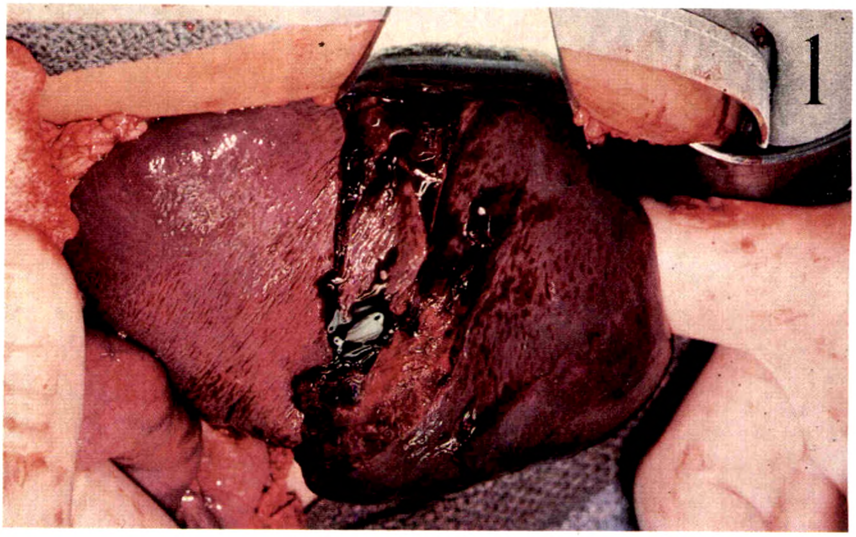
Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.
It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk. Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

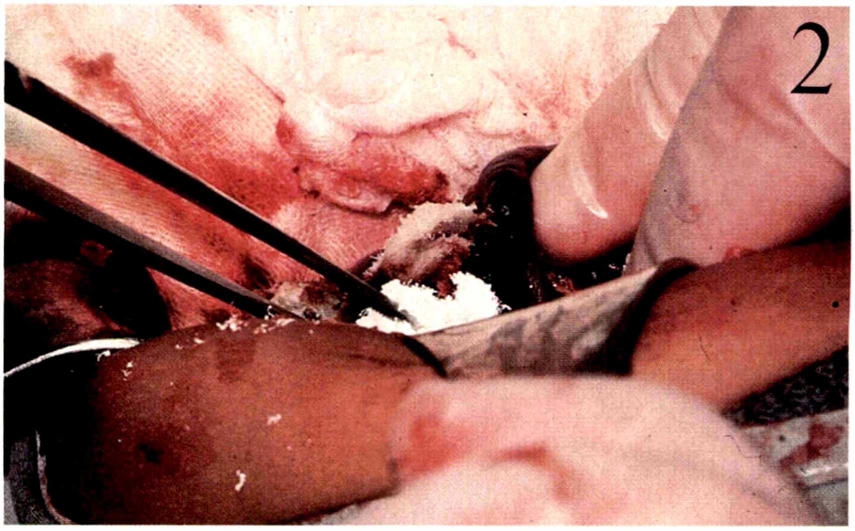
Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.
Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

A. H. Robins Company, Richmond, Va. 23220
A·H·ROBINS



1

Avitene® (MCH) at work: controlling parenchymal bleeding from a lacerated spleen in a child



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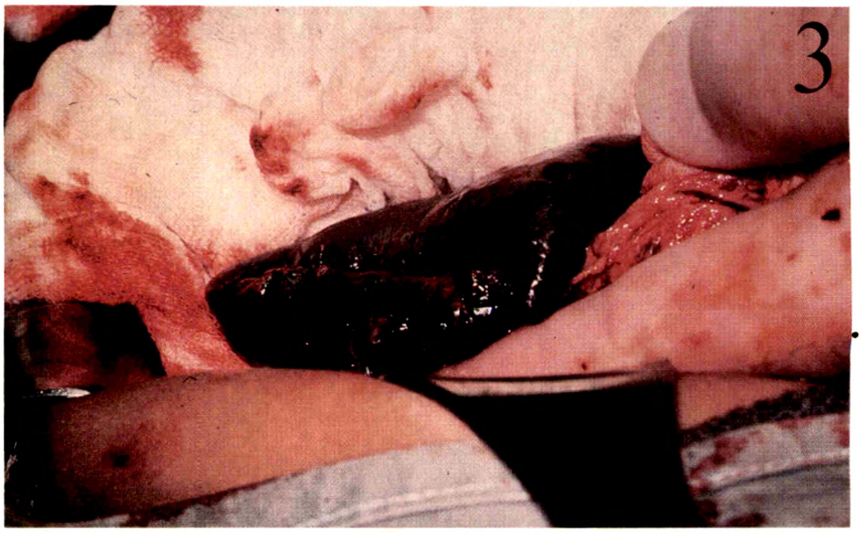


3

The spleen was nearly transected and a
artial splenectomy was performed.
emostatic mattress sutures were placed in the
lenic capsule but there was residual bleeding
om the splenic parenchyma.

Avitene® (microfibrillar collagen hemostat)
as applied directly to the bleeding surface
ith dry forceps. Using a dry sponge,
oderate pressure was maintained for
to 7 minutes.

With bleeding controlled, excess Avitene
as teased off the surface of the spleen.
he remaining portion of the spleen was not
sected. Recovery from partial splenectomy
as uneventful.

lease see facing page for brief summary.

Avitene®

Microfibrillar Collagen Hemostat

Avitene® (microfibrillar collagen hemostat), derived from purified bovine corium, differs physically, chemically, and clinically from other topical hemostats. Supplementing conventional hemostatic techniques, Avitene extends your range of options when surgical bleeding problems are encountered. In cases where sutures, cautery, or pressure are impractical or ineffective, Avitene...

...a modified natural collagen, triggers the normal hemostatic mechanism, and produces a normal (physiologic) clot

...adheres tenaciously, even to irregular bleeding surfaces

...controls generalized bleeding from soft, friable tissues and highly vascularized organs

...produces minimal foreign body response

...is effective in most patients receiving heparin or aspirin, and in those who are moderately thrombocytopenic.

Numerous clinical studies document the efficacy of Avitene in a wide range of surgical procedures. Reprints of these studies and films showing surgeons using Avitene (microfibrillar collagen hemostat) are available at your request. Films currently available include: **(1)** Six Demonstrations of Effectiveness; **(2)** Use in Partial Nephrectomy; **(3)** Use in Thoracic Surgery; **(4)** Use in Neurosurgery; and **(5)** Use in Bone Bleeding.

For further information, write:
Medical Director, Avicon, Inc., P.O. Box 85,
Fort Worth, Texas 76101.

AVICON Avitene® is distributed by
Alcon Laboratories, Inc.

HOW TO USE AVITENE®

Keep Avitene dry. Care must be taken to ensure that Avitene is kept scrupulously dry, as prolonged exposure to moisture will impair its hemostatic efficacy. It will adhere to any wet surface and should be applied only with dry smooth forceps.

Apply Avitene directly to the source of the bleeding. It is important that Avitene be applied directly to the source of bleeding. Otherwise Avitene may seal over the exit site of deeper hemorrhage and conceal an underlying hematoma. Surfaces to be treated should first be compressed with dry sponges, and then covered with Avitene. The amount required will depend on the force and severity of the bleeding.

Apply pressure with a dry sponge. It is then necessary to apply moderate pressure over the Avitene with a dry sponge. The period of time necessary will vary with the severity of the bleeding, and may range from a minute for capillary bleeding, to three to five minutes for brisk bleeding or arterial leaks. For control of oozing from cancellous bone, Avitene should be firmly packed into the spongy bone surface.

Remove excess Avitene. After five to ten minutes, excess Avitene should be teased away; this can usually be accomplished without initiating rebleeding. If breakthrough bleeding occurs in areas of thin application, additional Avitene may be applied. The amount required depends, again, on the severity of bleeding. In capillary bleeding, one gram will usually be sufficient for a 50 cm^2 area. Thicker coverage may be required for brisk bleeding.

Avitene® (microfibrillar collagen hemostat)

Description: Avitene is an absorbable topical hemostatic agent prepared as a dry, sterile, fibrous, water insoluble partial hydrochloric acid salt of purified bovine corium collagen.

Indications: Avitene is used in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

Contraindications: Avitene should not be used in the closure of skin incisions as it may interfere with the healing of the skin edges.

Warnings: Avitene is inactivated by autoclaving. Ethylene oxide reacts with bound hydrochloric acid to form ethylene chlorohydrin. This product should not be resterilized. It is not for injection. Moistening Avitene or wetting with saline or thrombin impairs its hemostatic efficacy. It should be used dry. Discard any unused portion. As with any foreign substance, use in contaminated wounds may enhance infection.

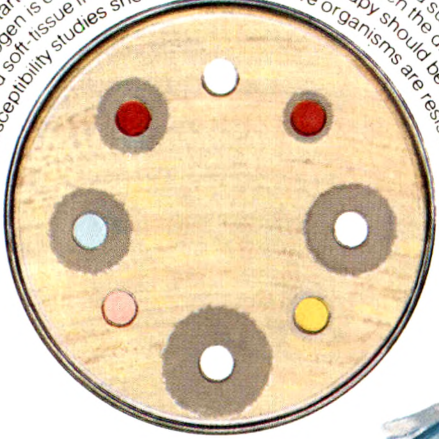
Precautions: Only that amount of Avitene necessary to produce hemostasis should be used. After several minutes, excess material should be removed; this is usually possible without the re-initiation of active bleeding. Avitene contains a low, but detectable, level of intercalated bovine serum protein which reacts immunologically as does beef serum albumin. Increases in anti-BSA titer have been observed following treatment with Avitene. About two-thirds of individuals exhibit antibody titers because of ingestion of food products of bovine origin. Intradermal skin tests have occasionally shown a weak positive reaction to BSA or Avitene but these have not been correlated with IgG titers to BSA. Tests have failed to demonstrate clinically significant elicitation of antibodies of the IgE class against BSA following Avitene therapy. Care should be exercised to avoid spillage on nonbleeding surfaces, particularly in abdominal or thoracic viscera. Teratology studies in rats and rabbits have revealed no harm to the animal fetus. There are no well-controlled studies in pregnant women; therefore, Avitene should be used in pregnant women only when clearly needed.

Adverse reactions: The most serious adverse reactions reported which may be related to the use of this drug are potentiation of infection including abscess formation, hematoma, wound dehiscence, mediastinitis. Other reported adverse reactions possibly drug related are adhesion formation, allergic reaction, foreign body reaction, subgaleal seroma (report of a single case).

How supplied: In 1 g and 5 g sterile jars of sterile microfibrillar collagen hemostat all contained in sealed can. Sterility of the jar's exterior cannot be guaranteed if can seal is broken. Content of jar is sterile until opened.

6/78

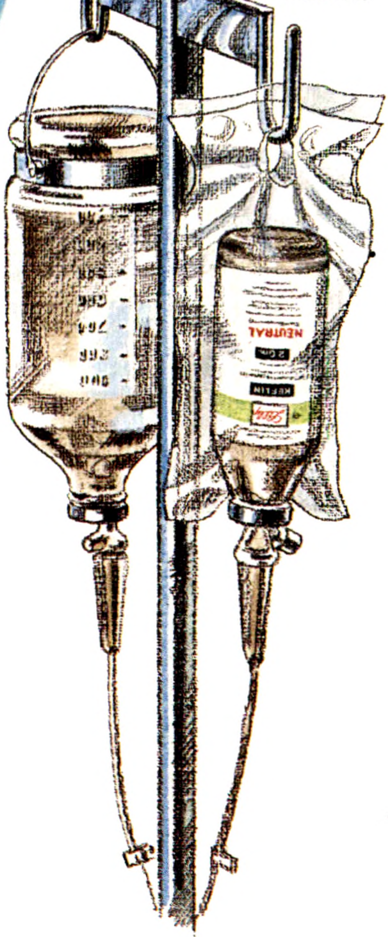
Appropriate cultures should be taken, but Keflin® (cephalothin sodium, Lilly) may be started before susceptibility results are obtained if you suspect the causative pathogen is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections.* Other antibiotic therapy should be instituted if susceptibility studies show that the causative organisms are resistant.

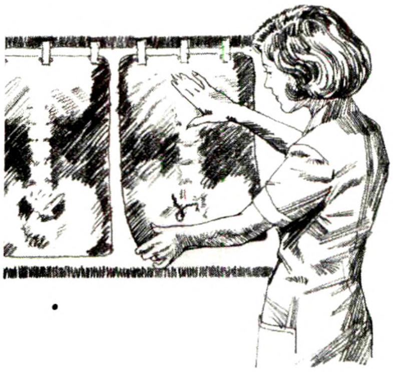


In the immunosuppressed patient, usual clinical signs and symptoms of infection may be missing or not clear. Hence, diagnosis and initiation of proper therapy become most urgent.

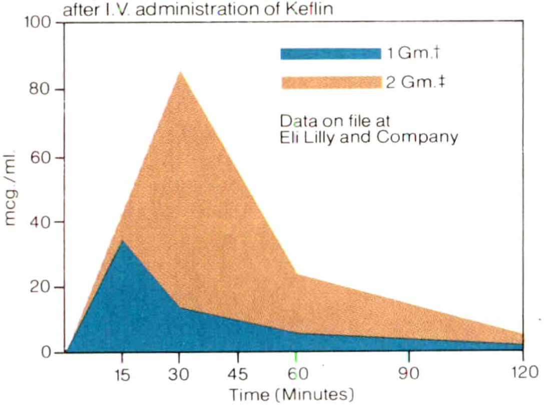
An initial loading dose of 1 to 2 Gm. of Keflin may be given regardless of the patient's renal status. Patients with impaired renal function should be placed on a reduced dosage schedule. Usual doses in such individuals may result in excessive serum concentrations.

Keflin may be administered I.V. or I.P. in dosages as high as 12 Gm. per day (in life-threatening infections).





Mean serum concentrations after I.V. administration of Keflin



†Administered to six patients by rapid I.V. infusion.

‡Administered to ten patients over a thirty-minute period.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

Please see opposite page for summary of prescribing information.

In serious skin and soft-tissue infections*

OFTEN USEFUL WHEN MOST NEEDED

As you know, skin and soft-tissue infections,* including peritonitis, may progress with alarming rapidity in patients with impaired host defenses . . . even to the point of becoming irreversible. Keflin can often be useful before the infection becomes irreversible . . . exactly when it is most needed.

Eleven years after its introduction, Keflin continues to be effective against most strains of gram-positive and gram-negative organisms commonly implicated in serious skin and soft-tissue infections.* Therefore, when you suspect that the pathogen involved is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections,* you may begin therapy with Keflin even while results of susceptibility studies are pending . . . and thus save precious hours for the patient. Keflin may be administered to infants and to patients with reduced renal function.

Keflin should be given cautiously to penicillin-sensitive patients.

It is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

* Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*.

Keflin® 2 Gm.† in 100-ml. ampoule

cephalothin sodium

Neutral

for Injection

† Equivalent to cephalothin

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin® (cephalothin sodium, Lilly), Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy – Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. (111475S)

Additional information available to the profession on request

Lilly

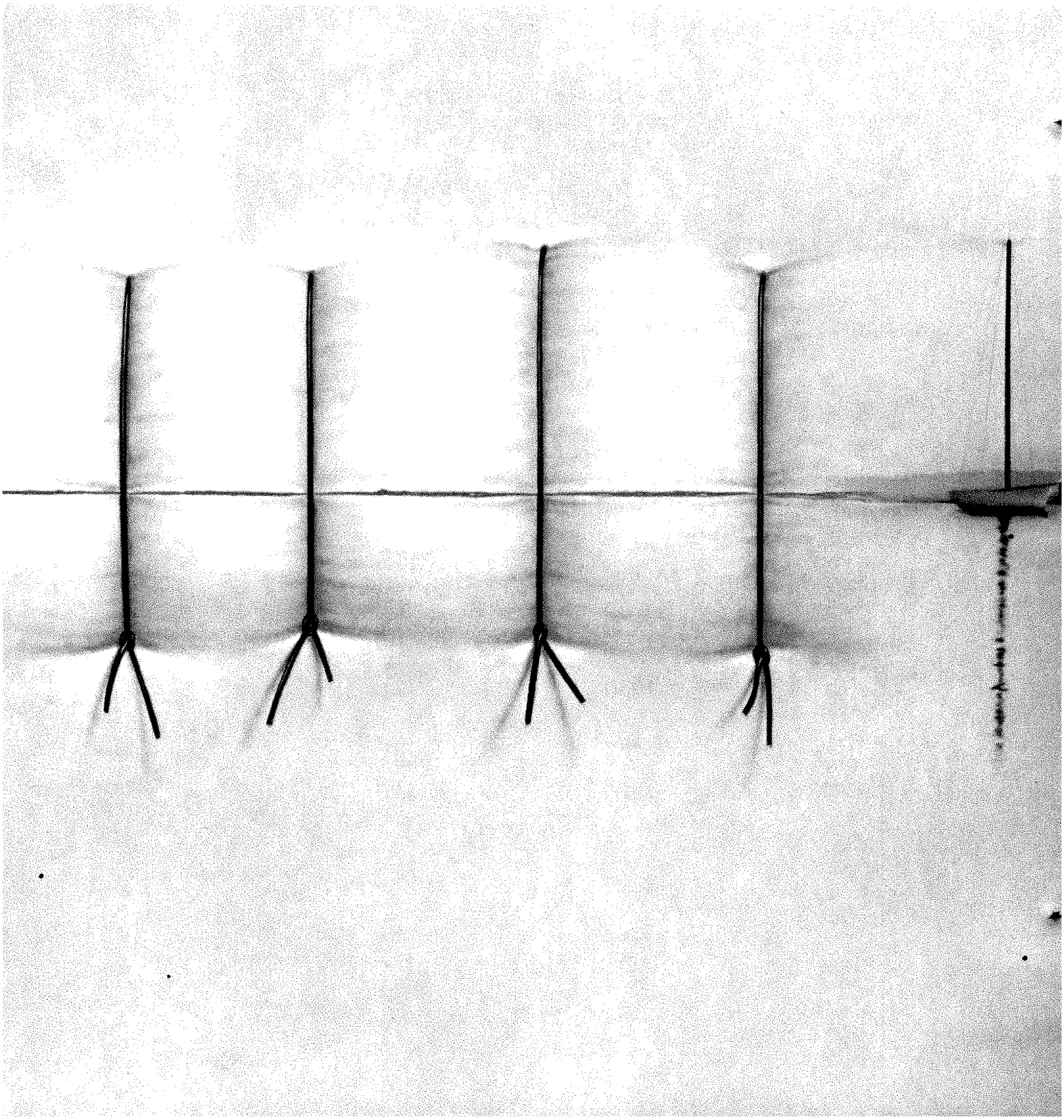
Eli Lilly and Company
Indianapolis, Indiana 46206

000395

'...it has long been recognized that anxiety, tension, agitation, and apprehension are all capable of increasing pain perception..."

Halpern, L. M.: Anxiety and pain in postoperative patients. Hospital Practice *(special report) January 1977, pp 31-3*

Following surgery... the perception of pain diminished



Vistaril® I.M.

(hydroxyzine HCl)

by Calm

- reduces the anxiety component of pain
- permits reduction in narcotic dosage
- controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

© 1977, Pfizer Inc.

Vistaril® I.M.

(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

**preoperatively
and
postoperatively**

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

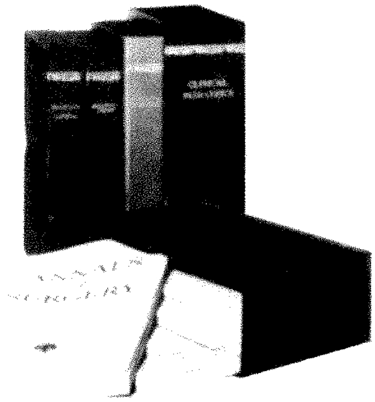
Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml–10 ml vials; 50 mg/ml–2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml–1 ml fill; 100 mg/2 ml–2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

Pfizer
LABORATORIES DIVISION
PFIZER INC.



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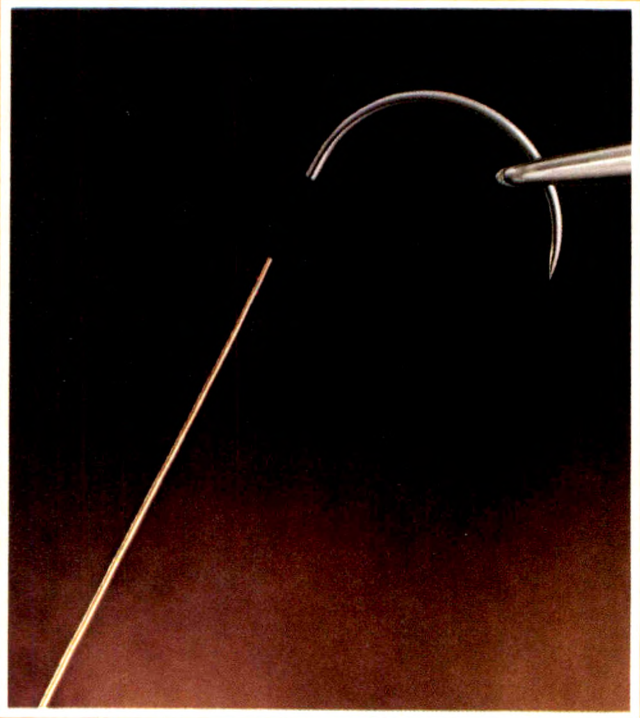
The needle/suture combination you've been waiting for...

SURGICAL GUT ON CONTROL RELEASE* NEEDLES



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the closing word

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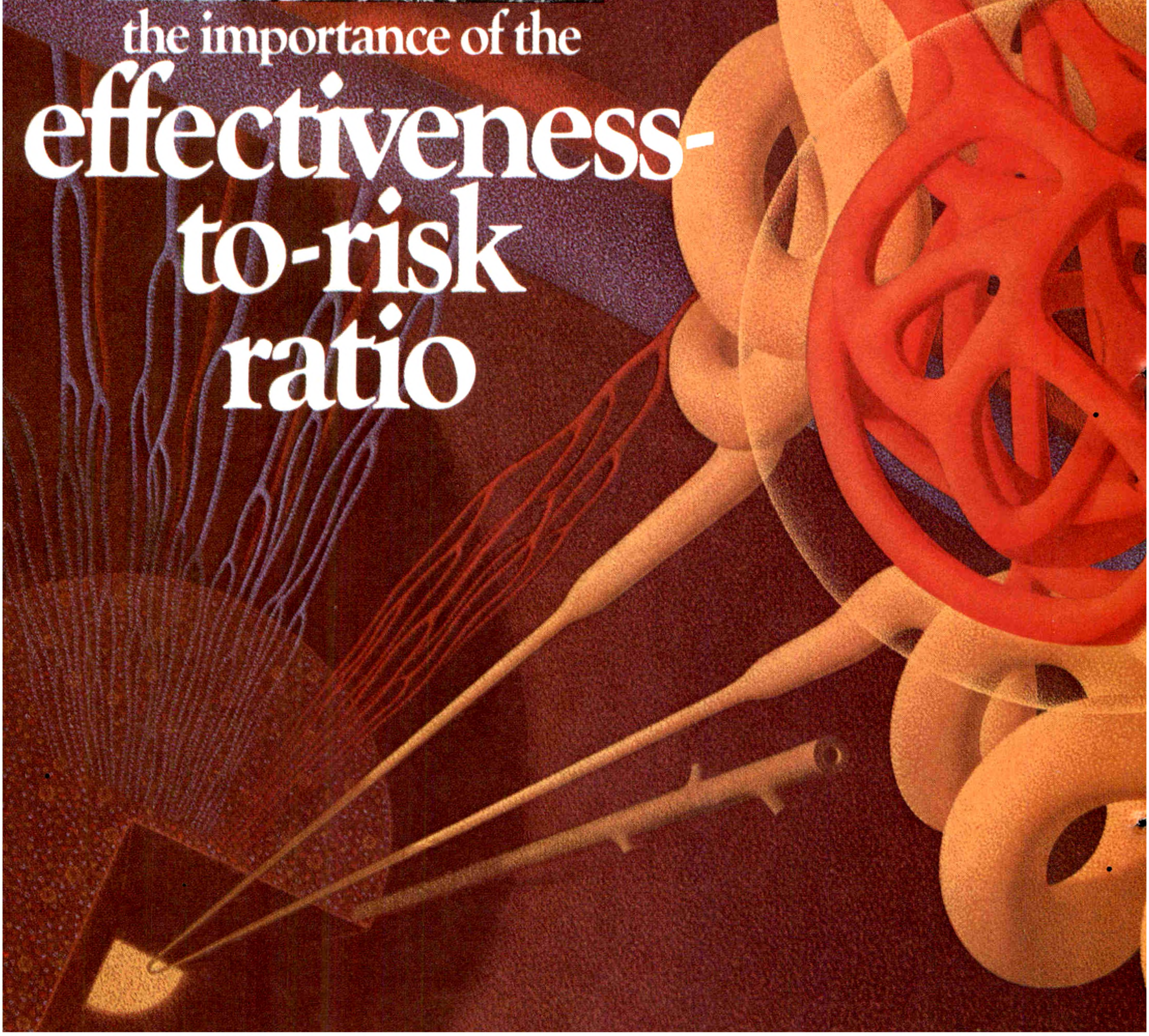
Selecting an aminoglycoside:

In patients with serious bacterial infection, the choice of antibiotic therapy is usually made on the basis of the effectiveness-to-risk ratio. This consideration is particularly important when an aminoglycoside antibiotic is indicated.

The activity of Nebcin® (tobramycin sulfate, Lilly) against a wide range of gram-negative organisms is now well known. A review of worldwide literature shows "that tobramycin has significant antibacterial activity and that it is the most potent of all aminoglycosides against *P. aeruginosa*. The antibacterial

Brush-border membrane of proximal tubule (11,400×).

the importance of the effectiveness-to-risk ratio



activities of tobramycin and gentamicin against members of the Enterobacteriaceae are comparable, with each agent possessing slightly greater activity than the other against selected strains of any species."[1]

Nebcin is indicated in the treatment of

- septicemia
- serious lower respiratory infections
- gastrointestinal infections, including peritonitis
- serious complicated and recurrent urinary tract infections
- serious skin, bone, and soft-tissue infections, including burns

caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus* sp. (indole-positive and indole-negative), *Providencia*, *Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

The proximal tubule

The proximal tubule is the site in the renal system where aminoglycosides produce nephrotoxicity.

An investigator has studied the urinary excretion of alanine aminopeptidase, a principal enzyme of the brush-border membrane of the proximal tubule.[2] Levels of the enzyme become elevated in the urine as a result of toxic lesions in acute tubular necrosis or of inflammatory processes in the kidney, such as rejection crisis. In measurements of the effect of aminoglycosides (administered for three consecutive days) on the excretion of this enzyme by healthy humans, tobramycin appeared to have a minimum effect on the brush-border membrane.

Another investigative team has studied the relationship between tissue concentration and toxicity.[3] The toxicity of aminoglycosides may be related to the degree of their binding to tissue. Hence, aminoglycosides that accumulate less may be less nephrotoxic.

All aminoglycosides are potentially nephrotoxic and ototoxic. Therefore, patients should be monitored closely when aminoglycosides are being used. Patients with impaired renal function, the elderly, those with underlying disease, those with prior exposure to potentially nephrotoxic agents, and those with poor host resistance are at special risk. During clinical trials in 3506 patients treated with tobramycin, investigators reported drug-related nephrotoxicity in 1.5 percent (53 patients).[4]

In view of the effectiveness of Nebcin and the relatively low risk of nephrotoxicity, tobramycin can be an appropriate choice for patients requiring aminoglycoside therapy.

References

1. J. Infect. Dis., *134* (Supplement):S3, 1976.
2. J. Antimicrob. Chemother., *4* (Supplement A):23, 1978.
3. J. Antimicrob. Chemother., *4* (Supplement A):53, 1978.
4. Med. J. Aust., *2* (Special Supplement):22, 1977.

◆ I.M./I.V.

tobramycin/Nebcin®

tobramycin sulfate

80 mg* in 2-ml ampoules

*Equivalent to tobramycin.

Please see following page for a brief summary of the prescribing information.

Nebcin® ◆ I.M./I.V.
tobramycin sulfate

Summary of Prescribing Information

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: See WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility that prolonged or secondary apnea may occur should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

The usual duration of treatment is seven to ten days.

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg/kg/day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg/kg/day administered in three or four equal doses. This dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg/kg/day may be given in two equal doses every 12 hours.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg/kg, subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.* To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg/kg q (6 × serum creatinine) h

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of 20 to 60 minutes.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function
(Dosage at Eight-Hour Intervals)

For Patient Weighing		Usual Dose for Serious Infections 1 mg/kg q 8 h (Total, 3 mg/kg/day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg/kg q 8 h (Total, 5 mg/kg/day)	
kg	lb	**mg/dose q 8 h**	**ml/dose†**	**mg/dose q 8 h**	**ml/dose†**
120	264	120 mg	3 ml	200 mg	5 ml
115	253	115 mg	2.9 ml	191 mg	4.75 ml
110	242	110 mg	2.75 ml	183 mg	4.5 ml
105	231	105 mg	2.6 ml	175 mg	4.4 ml
100	220	100 mg	2.5 ml	166 mg	4.2 ml
95	209	95 mg	2.4 ml	158 mg	4 ml
90	198	90 mg	2.25 ml	150 mg	3.75 ml
85	187	85 mg	2.1 ml	141 mg	3.5 ml
80	176	80 mg	2 ml	133 mg	3.3 ml
75	165	75 mg	1.9 ml	125 mg	3.1 ml
70	154	70 mg	1.75 ml	116 mg	2.9 ml
65	143	65 mg	1.6 ml	108 mg	2.7 ml
60	132	60 mg	1.5 ml	100 mg	2.5 ml
55	121	55 mg	1.4 ml	91 mg	2.25 ml
50	110	50 mg	1.25 ml	83 mg	2.1 ml
45	99	45 mg	1.1 ml	75 mg	1.9 ml
40	88	40 mg	1 ml	66 mg	1.6 ml

†Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules (Vials) Nebcin® (tobramycin sulfate, Lilly), Injection, 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1 and Traypaks™ (multivial cartons, Lilly) of 25.

Ampoules (Vials) Nebcin, Pediatric, Injection, 20 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1.

Hyporets® (disposable syringes, Lilly) Nebcin, Injection, 60 mg (equivalent to tobramycin) per 1.5 ml, 1.5 ml, and 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, in packages of 24.

Each ml also contains 5 mg phenol as a preservative, 3.2 mg sodium bisulfite, 0.1 mg edetate disodium, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [030476C]

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46206.

Lilly

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

800646

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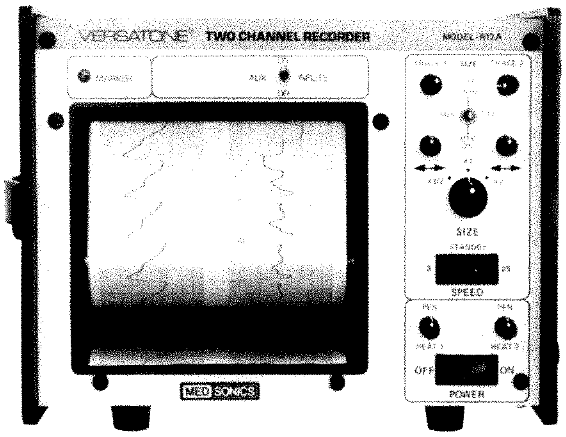
*An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

VERSATILE INSTRUMENTS FOR THE VASCULAR LABORATORY

VERSATONE® BI-DIRECTIONAL DOPPLER MODEL D9 Used with one of four plug-in probes, MedSonics Bi-directional Doppler employs ultrasound and the Doppler shift principle to detect blood flow and to distinguish the direction of flow. It provides explicit separation of advancing and receding blood flow, even in the presence of simultaneous flow in two directions. The Model D9 has a variety of outputs, including built-in loudspeaker, stereo headphones, tape recorder jacks, and calibrated outputs for graphic recording. Three pencil type probes (5MHz, 8MHz and 10MHz) and one flat probe (5MHz) suitable for taping in place are available.

VERSATONE® BI-DIRECTIONAL DOPPLER
VERSATONE® TWO CHANNEL RECORDER
MED SONICS



VERSATONE TWO-CHANNEL CHART RECORDER MODEL R12A The VERSATONE two-channel Chart Recorder is used to chart the Doppler signals of forward and reverse blood flow from the Model D9 Bi-directional Doppler. This Recorder can also chart an ECG signal, by itself or mixed with a Doppler signal. An optional, built-in ECG preamp is available. In addition, the R12A accepts many other "high level" physiologic signals you may wish to record, including those obtained from MedSonics PPG equipment.

PHOTOPULSE® PPG SENSORS AND MODEL PA13 ADAPTOR The PHOTOPULSE photoplethysmograph (PPG) provides a sensitive means of detecting blood volume changes in the microcirculation close to the skin's surface. It may be applied to those parts of the body with good capillary beds, including digital pads, where it can be used to monitor pulse. The PPG also is used in a non-invasive procedure to detect significant obstruction of the extracranial internal carotid artery. Two PHOTOPULSE sensors are placed under a head band over each supraorbital area to record volume changes that occur when a series of compression maneuvers are carried out.

The PA13 adaptor allows the use of two PPG sensors with the R12A recorder or with other laboratory chart recorders.

For more information on these and other instruments for the vascular laboratory, call or write:

MEDA SONICS

MedSonics, Inc. • 340 Pioneer Way, P.O. Box M • Mountain View, CA 94042
Toll-free telephone 800 227-8076 • In California, call collect (415) 965-3333
Telex: 33-4448 • Cable: MEDASONICS

Not All Postsurgical Patients Should Receive Potent Injectable Narcotics

CAUTION

In patients with decreased respiratory reserve, morphine and related narcotics must be used with great caution.

High Risk Patients

- Severely obese patients
- Patients with kyphoscoliosis
- Patients with chronic cor pulmonale
- Emphysematous patients
- Asthmatic patients

Many patients with such conditions are already utilizing compensatory mechanisms, such as increased respiratory rate. Many may have decreased sensitivity to elevated plasma CO_2 stimulation. The further imposition of the depressant effects of narcotics can be disastrous.

Consider

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of

pentazocine lactate injection, NF

Talwin shows infrequent occurrence of certain adverse effects* as:

- Respiratory depression (see below)
- Circulatory depression
- Shock
- Tachycardia
- Urinary retention

The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g. from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

There have been instances of psychological and physical dependence on Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. Patients with a history of drug dependence should be under close supervision while receiving Talwin. In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

For immediate pain control without many of the risks of narcotic analgesics:

Talwin®

30 mg. parenterally q. 3 to 4 hours.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

*See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of
pentazocine lactate injection, NF

Relieves pain of a moderate to severe nature.

Please consult full prescribing information before prescribing. A summary follows:
Talwin is intended for the relief of moderate to severe pain. 30 mg. is usually as effective an analgesic as morphine 10 mg. or meperidine 75 to 100 mg. The duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15 to 20 minutes after intramuscular or subcutaneous injection and within 2 to 3 minutes after intravenous injection. Talwin is a weak narcotic antagonist with sedative activity. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

CONTRAINDICATION

Hypersensitivity to pentazocine.

WARNINGS

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, animal studies have demonstrated that Talwin is tolerated less well subcutaneously than intramuscularly.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

PRECAUTIONS

The possibility that Talwin may cause respiratory depression should be considered. Talwin should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

ADVERSE REACTIONS

The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.
Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face, toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

Adults, Excluding Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg.

See Warnings in package insert as to recommended sites and routes of administration.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

OVERDOSAGE

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

HOW SUPPLIED

Uni-Amp®—Individual unit dose ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in boxes of 25.

Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in (nested) boxes of 25.

Each 1 ml. contains pentazocine lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing pentazocine lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

4004

Panel on National Health Insurance

Introduction

DAVID C. SABISTON, JR., M.D.*: In introducing the subject of National Health Insurance, it seems appropriate to recall the admonition of the great philosopher Santayana: "Those who cannot remember the past are condemned to repeat it." There are many examples of National Health Insurance plans which have been in practice elsewhere for a number of years and allow us the privilege, and indeed the obligation, to determine their outcome. Of great importance is the effect of these plans on quality of medical care, their effect on the public, the changes which have occurred in the medical profession and their influence upon the national economy. Much is to be learned from these past experiences in other countries and, in point of fact, it would be foolhardy to repeat misadventures which are already a matter of historic record.

In an effort to place in perspective the history of National Health Insurance in the United States, it should be emphasized that as early as 1912 a group of leaders concerned with this problem concluded that, if the middle class and the poor were to have access to good medical care, a health care insurance program should be enacted sponsored by the Federal Government. It is interesting that the AMA supported this view for a number of years. In 1932 a document summarizing this study was published entitled *Medical Care for the American People—The Final Report of the Committee on the Costs of Medical Care*, being supported by eight foundations with a broad membership of both professionals and laymen. The single issue concerned the financing of health care for the nation, but in the end there was much disagreement among the participating groups and little of significance resulted.

The issue of socialized medicine re-emerged in 1939 with introduction of the Wagner-Murray-Dingell Bill, a proposal submitted to the Congress which gained much public attention. However, this campaign failed to attract enough support to secure passage, and ultimately the issue lost momentum. The details of these efforts are carefully chronicled in Hirshfield's *The Lost Reform—The Campaign for Compulsory Health Insurance in the United States from 1932 to 1943*, a valuable treatise concerning the many issues during that decade.

In the late 1940s and early fifties, President Truman cast his support behind a revised National Health Insurance program. Once again, the opposition, led primarily by the AMA, proved formidable. Unable to enact such legislation, toward the end of his Administration President Truman appointed a Committee to report on *alternative* routes that the Federal Government might follow to improve the nation's health care. The President's Commission on Health Care Needs of the Nation, often called the Magnuson Commission, recommended that, since changing the financial base was not practical, the Federal Government should increase its flow of resources into the health care system to expand investments in research and facilities. Thus, two major pieces of legislation emerged, the Hill-Burton Act supporting construction of a number of hospitals throughout the country and, secondly, the National Institutes of Health legislation which greatly augmented federal support for biomedical research. In 1960, the Congress passed the Kerr-Mills Act, making funds available to the states to enable the delivery of medical care to low income, aged persons. This ultimately led to the passage during the Johnson Administration in 1965 of the Medicare and Medicaid bills, bringing the issue to the present.

If there is a determined effort to prevent past mistakes, it is essential that objective reviews be made of the experiences in other countries of comprehensive National Health Insurance programs. Gunnar Biorck, Professor of Medicine at the Karolinska Institute in Stockholm, is a distinguished international physician and is so recognized everywhere. In a recent publication entitled *How to be a Clinician in a Socialist Country*, he states his views quite concisely by saying that in Sweden "the impact on the freedom of the medical profession on the patient–physician relationship is considerable and destructive to the concepts of a free profession."

One feature which Biorck emphasizes is the fact that administrators have assumed control and that the machinery has thus lost its lubrication. He summarizes by saying, "Looking at another aspect of the socialization of medicine in my country, the introduc-

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* From the Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710.

• Presented at the Annual Meeting of the American Surgical Association, April 26–28, 1978, Dallas, Texas.

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tion of these various regulatory processes has resulted in a cancerous growth in the number of medical administrators at all levels of incompetence."

Professor Biorck then proceeds to describe the steps taken by the government in Sweden to subjugate the profession in this order:

1) Introduce compulsory health insurance and bind physicians to working rules, fee schedules, and paper work.
2) When this is established procedure, bind physicians to a fixed salary for a regulated office week, that is, make them all civil servants.
3) Forbid professional activities outside regulated working hours. (Activities in capacities other than as physicians may be tolerated. No limitations are set on the activities of "quacks," but physicians are forbidden to offer services under this pretense).
4) Increase the output of medical schools to produce an excess of physicians, thus lowering their income level and standard of living.
5) Centralize all postgraduate training and abolish the individual's free choice of future specialty.
6) Abolish the patient's free choice of physician through systems of geographical adherence to certain hospitals and health centers.
7) Introduce political steering of universities and medical schools and of research granting organizations.
8) Abolish grades and marks in graduate and postgraduate studies and de-emphasize professional merits in the selection for future posts.
9) Let appointments to senior posts be made by local political bodies.
10) Socialize and standardize the production and distribution of drugs.
11) Computerize all patient information in one nationwide computer.

Finally, Biorck laments that "the freedom to choose the area of one's work, and the existence of medicine as an *art* cherished by people who could not help doing what they loved and loving what they did—the socialist strategy in my country, so far, seems to aim at closing this last reserve." He concludes this keynote address with a statement which bears careful attention in the United States: "It is necessary to take such effects into account in the planning for nationalized health services anywhere in the world."

One might ask if Professor Biorck's position is a politically unpopular one in Sweden. The fact is, however, that shortly after presenting this courageous address at the University of Chicago, Professor Biorck was elected a member of the Swedish Parliament, the only physician in that body.

A long standing friend and honorary member of this Association, Philip Sandblom, formerly Professor of Surgery at the University of Lund, summarized his views concerning Sweden's National Health Insurance Program before the Board of Governors of the American College of Surgeons stating:

> All hospital doctors now become 100 percent salaried employees with regulated working hours. Capacity and ability are not rewarded. The salary is related to the position held, based on a 40-hour week, with extra payment for more hours, but there is no difference with respect to the kind of specialty or the work load. The salary is thus related to the amount of time spent in the hospital, irrespective of the kind of work performed.
>
> The older generation of surgeons was accustomed to hard work and did not count the hours. The younger generation has begun to realize the futility of high incomes in a situation where three-fourths of it is cut away by extremely high progressive taxation, and so they begin to put a greater value on their free time. This has resulted in a drive for shorter working hours, which is unworthy of the medical profession and contrary to its ancient ethics.

Two years ago at the meeting of the American section of the International Society of Surgery in New Orleans, Professor Charles DuBost of Paris reviewed the status of government medicine in France. He emphasized the many problems which practicing physicians had encountered with the system and repeated over and over the word "mediocrity—mediocrity—mediocrity," indicating that this had become the hallmark of the entire program, and he thought much to the disservice of the French people.

Since they have had 30 years' experience with socialized medicine, there is much to be learned from the record now available in the British Isles. In 1947 the labor unions, working through the Labor Government of Prime Minister Attlee, and particularly with the labor leader Aneurin Bevan, enacted the National Health Service Act. The government assumed control of nearly all hospitals and placed most specialists on salaries. Early experience with the program was by and large regarded as favorable, and there is no doubt that a majority of the British medical profession cooperated wherever possible in making the system a success. With the passage of time, however, increasing problems arose and Sir George Pickering, the noted Regius Professor of Medicine at Oxford, recently lamented in a Nuffield Lecture the decline in learning and in professional etiquette which has occurred. In this address, he emphasized the fact that, with the growth of the trade unions, social change occurred in Britain, since the object of each union was to obtain the greatest slice of the national gross product for its own members without consideration for others. Its weapons were, he said, the *strike* and the "go-slows" which were bringing management and government to their knees. Sir George feared that all the signs pointed to the fact that medicine seemed apt to conform to this outlook and behavior. He could only hope that the National Health Service might be removed from political influence, and that the leaders of the profession might guide it back towards its traditional role of a learned profession and prevent its becoming a technical trade union.

Most are familiar with the section in *The New England Journal of Medicine* entitled "By the London Post," authored by John Lister, Dean of the British Postgraduate Medical Federation of the University of London. He has long been a very thoughtful spokesman and collects data carefully before drawing conclusions. Originally a supporter of most aspects of the National Health Service, within the past several years he has recognized its ever increasing defects. In a recent letter he stated:

> I personally think it is very sad to see an enlightened scheme getting into serious trouble from many points of view. The early years of the N.H.S. were marked by a considerable degree of collaboration between the health department and the medical and nursing profession, both of whom showed good will in running the service. The reorganisation of the N.H.S. in 1974 with its increasing numbers of administrators and increasing difficulties in decision making was a serious setback. Furthermore, the abrasive attitude of Mrs. Barbara Castle when she was Secretary of State for Social Services has alienated much of the good will of the medical profession, who now feel that they have a hostile employer.
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> The attack on private patients was a major factor in creating this situation. The serious financial state of the country in the last few years has aggravated the situation and led to stringent economy and reallocation of resources with the politicians deciding the priorities for expenditure on health. The rise of professionalism in the allied health services and the misuse of trade union power, particularly in ancillary hospital workers, has led to loss of medical dominance. While many of us realise that complete dominance cannot reasonably continue in the present social environment, there is no doubt that the erosion of medical influence has had a serious effect on the whole service.

John Lister's message is very clear, and it is apparent that each of his points is deserving of thoughtful consideration in formulating future plans in this country.

Eoin O'Malley, Professor of Surgery at University College, Dublin, in a recent address in this country entitled "The Doctor's Dilemma" said, "In Ireland, 85–90% of the population is entitled to free hospital service, free being a euphemism to indicate that the service is provided for by taxation." He then reviewed many problems which he had encountered, including the limited number of operations which can now be performed, the long waiting lists which have become commonplace, and the economic necessity for budgetary restrictions to select patients for operation—leading to an admonition to Americans: "The scene is set for the doctor's dilemma of the future. On my side of the Atlantic the curtain has started to rise; I can only hope that on your side the play may never reach the stage."

Another detracting feature of the British National Health Service is the economic burden it places upon the government and the people. In two recent seminars on "The Future of the Private Sector in Medical Care and Education," sponsored by William G. Anlyan at Duke University, this subject among others was reviewed. A number of the participants commented upon the open-endedness of total government health programs leading to the statement of Mr. J. Enoch Powell in Britain that "in a system of free medicine, the demand for free care is infinite," a concept which is now termed Powell's Law.

Many here will recall that in his Director's Memo entitled "The British National Health Service," written after attending a London seminar on the subject, C. Rollins Hanlon said: "The dangerous oppression of a swollen bureaucracy needs no emphasis. The critical challenge to American surgery is how to maintain quality of surgical services without splitting the profession as one sees it so painfully demonstrated in Britain. Accessibility to services may well have been improved, but the casualty of that alteration is quality."

There is also a lesson to be learned from Canada, as recently stated by Philip R. Bromage who recently emigrated to the United States because of the situation of government medicine there. For the previous seven years Dr. Bromage had been Professor and Chairman of the Department of Anesthesiology at McGill University and Chief of Anesthesia at the Royal Victoria Hospital in Montreal. He is now Professor of Anesthesia at Duke and writes:

> Socialization of Medicine in Canada is based on Federal funding and matching Provincial Funds.

Each Province, being autonomous in matters of Health and Education, has been free to develop its own pattern of health care delivery.

The Province of Quebec modelled its scheme on the Castonguay Report of 1968, and its socialization was very thorough. A series of bills were passed in 1970 and 1971 with the following results:

1) *A comprehensive health and hospitalization plan*, for all citizens.
2) *Destruction of the free market in health care delivery*, by creating a state (Provincial) monopoly in health insurance. All private health insurance was outlawed, except in minor areas uncovered by the government scheme.
3) *Containment of the medical profession in a) social, b) professional, c) fiscal matters, and d) direction of labor.*
   a) Hospital management was placed in the hands of lay committees, and the medical profession was virtually removed from the process of decision-making.
   b) The medical profession was subjected to industrial-type legislation. Negotiations with the government had to be conducted through the Federations of Medical Specialists, and the Federation of Omnipractitioners (*i.e.*, G.P.s). These were union-type organizations set up for the purpose of negotiating terms and conditions of services.
   c) A fee-for-service system was negotiated in which every type of medical act was described, priced and coded for computer purposes. The resulting data bank was extremely comprehensive, and it was used effectively in adjusting scales of remuneration, both in absolute terms, and relatively between the various specialties.
   d) Direction of labor. This has been under consideration, but not implemented as yet. Discussions proceed about the advisability of drafting newly qualified M.D.s to underdoctored areas, as partial solution to maldistribution problems.
4) *Cost Containment and Reduction of Acute-Care Beds*. Hospital global budgets have failed to match rising nonprofessional labor costs in many instances. This has resulted in closure of about 20–25% of acute care beds in many of the major teaching hospitals (the Royal Victoria Hospital, Montreal, had about 200 of its 800 beds closed when I left last year). There is promise of a comparable *increase* in chronic care beds, but so far this has not been implemented. The phenomenon of reduction of acute care beds appears to be part of a deliberate policy, and is in accord with patterns of socialized medicine elsewhere.

   A policy of regionalization–rationalization has produced some positive results, particularly in the area of obstetrics and neonatal care. Some small units have been closed down, and services have been concentrated in fewer but larger and more effective facilities.

In summary, a comprehensive health plan has brought many benefits to the public at large in the Province of Quebec. Within this scheme, government policy appears to be emphasizing the importance of public health and chronic care, while de-emphasizing the importance of traditional acute care. At the same time, the medical profession has been removed from the decision-making process of health care management, and the M.D. has been reduced to the status of a skilled artisan (entitled a "health professional"). At present, he is adequately remunerated, but the quality of the medical environment in which he works appears to be deteriorating.

The most updated figures for the present status of health care insurance in the United States were recently provided by the National Blue Cross–Blue Shield and the American College of Surgeons. The data show that Blue Cross–Blue Shield currently covers 85 million of the present 213 million population in this country. In addition, private insurance companies have in force a total of 86 million health policies, some of which represent partial coverage and in other instances these policies are supplementary to coverage by Blue Cross. HMOs are now responsible for the health needs of 6,330,000 citizens; Medicare covers 25,500,000 and Medicaid provides care for 21,500,000. Thus, the total health care coverage by one form of insurance or another is quite impressive.

Is it not appropriate to ask if the *real problem* is not Government sponsored insurance, preferably managed through private sources, *for those citizens who have either inadequate or no coverage*, and in addition to institute health insurance for those with *catastrophic illnesses*? Would it not be much preferred to take this approach and attack the part of the system which *needs* attention rather than revamp the coverage of the great majority of U.S. citizens who already have well documented adequate health insurance? It would appear logical to direct attention to the *indigent*, currently estimated to number approximately 20–25 million of the total 218 million population. If to this a comprehensive policy is added to provide federally guaranteed coverage for catastrophic illness to all citizens, the issue will have largely been solved.

Currently the United States devotes approximately 9% of the gross national product to the health care industry, a complex which employs one out of 20 of the workers in the nation. The tremendous escalation in cost of medical care offers a further deterrent to a comprehensive national health scheme directed by the Federal Government. One need only review the experience of the government with Medicare and Medicaid. Since their introduction in 1965, total federal expenditures for health care have increased approximately eight-fold, from approximately $5–$40 billion annually in 1976.

It is widely recognized that further increases in the federal health dollar are apt to seriously affect the overall economy and certainly the inflationary spiral. Eli Ginzberg, the noted Columbia economist, has placed the entire political and fiscal situation in sharp profile in a recently published monograph entitled *Limits of Health Reform*. He emphasizes that the American people have taken extreme positions only when the system comes under *great* challenge and cites, for example, that when Congress was thoroughly annoyed with the arrogance of the monopolies in 1890 it passed the Sherman Antitrust Act. Similarly, the banking difficulties in 1907 led to the Aldridge Commission and the passage of the Federal Reserve Act in 1913. Moreover, it required the Great Depression of the 1930s to make possible the unprecedented government acts which characterized the New Deal. However, at present Ginzberg feels that it is out of the question to plan a federal bureaucracy of the size, scope, and expense of a National Health System. To add further to this problem, in a recent report to the House Ways and Means Committee, the Comptroller General of the United States evaluated performance of the Social Security Administration compared with that of private fiscal intermediaries in dealing with institutional providers of Medicare services. The data which were obtained are of much interest and show how much more it appears to cost the Federal Government for identical services. The cost of processing a bill by the Division of Direct Reimbursement of the Social Security Administration is $9.23 per bill, while the total cost for this processing per bill for the Maryland Blue Cross is $4.94 and the Chicago Blue Cross is $5.18 for the same service.

In a recent editorial concerning the debate over whether or not the VA Hospital system should be absorbed into the private sector, Arnold Relman, editor of *The New England Journal of Medicine*, posed a very direct question both to the Federal Government and to the American people when he asked, "The political realities may very well ordain otherwise, but wouldn't it be a triumph for common sense if our government were to approach the regulation and reform of its own Veterans Administration hospital system with the same zeal that characterizes its present plan for the private sector?"

In summary, before embarking upon a federally sponsored program of National Health Insurance, Relman's question and many others like it require adequate and convincing answers. At this point, it seems likely that the nation will do well to interfere minimally with the 80-plus % of Americans whose health care costs are already largely covered by private insurance and simultaneously to devise a plan to fully insure by federal support both the *indigent* and the total population for *catastrophic illness*. Such an approach appears likely to provide a very acceptable solution.

Current Dilemmas in National Health Insurance

DAVID A. HAMBURG, M.D.†: I am not an expert on national health insurance, but I have been fortunate during the past few years to be President of an organization that does have a good many experts on national health insurance. I am indebted to them for an overview of national health insurance issues and an appreciation of the diversity in this very complex and perplexing area; I am especially indebted to three of them, Robert Ball, Alain Enthoven, and Stanley Jones. They have helped me greatly.

The Institute of Medicine has not done a formal study of national health insurance *per se*, although we have studied some of the basic dimensions of health policy that would be pertinent to any national health insurance scheme.

A word about the nature of the IOM: It is a private organization, not governmental. It is a semiautonomous part of the National Academy of Sciences, which is private, but the Academy has two charters, one going back to Abraham Lincoln, and one to Woodrow Wilson, which in effect make it close to government, make it a vehicle for advice from the scientific community to the government, that is, formal studies on topics that have relatively high technical content. In recent years, the closely related National Research Council has devoted much of its effort to science-related questions of public policy.

The Institute itself is very broadly composed of the entire range of health sciences and health professions, about as broadly as that can be construed, and has a full-time staff in Washington that articulates with the membership throughout the country. It is divided

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into six divisions that are concerned with health services, science policy, health resources and manpower, disease prevention, legal and ethical aspects of health, and international health. So, you see, we deal with the very large, interdisciplinary real world and nearly intractable problems.

What we strive for is to get as objective analysis as is humanly possible—what Enthoven calls "the facts about the facts"—disciplined formulations of options, assets and limitations of each option, multiple perspectives on many-faceted problems; in other words, policy research in health. And when I mention that phrase, I am reminded of a very astute remark of Will Rogers, ostensibly a humorist, but actually a political philosopher.

Will Rogers said he was called in by President Wilson for advice about the German U-boat threat during World War I, and he said he'd study the problem. Then Rogers came back with a proposal: to bring the Atlantic Ocean to a boil and let the water evaporate; that would force the U-boats to the surface where they could be readily destroyed. Wilson said to him: Well, for God's sake, how would you bring the Atlantic Ocean to a boil? And Rogers said: Mr. President, I advise on policy. That is a technical detail. So we advise on policy at the IOM.

Is there a plausible rationale for national health insurance? Historically what kinds of justification have been given? What is national health insurance all about?

I am really talking about national health insurance, and not about a nationalized scheme, as in the case of Sweden and England. It seems highly unlikely to me that in the lifetime of anybody in this room, even if there are some young surgeons in this room, that we would have a fully nationalized scheme. National health insurance of a distinctively American variety may eventually come to pass, and even though the objectives as between the U.S. and other industrialized countries would tend to be similar, the style would surely be different. We do have a history of social invention in this country that often leads to distinctive innovations to deal with national concerns.

In any case, the most important objective of national health insurance is to make sure that everyone can get good medical care at a price that can be afforded. So, in essence, there are three considerations that are fundamental, as I see it: access, quality, and cost.

National health insurance assumes that medical care is truly worth having, that is, the validity question. In contrast to 20 years ago, voices are now heard which say that medical care is worth very little. There is a nihilistic streak which has caught on to a certain extent in the public that medical care is enormously overrated.

It is, however, striking that, in my experience, even the most skeptical critics of American medicine tend to seek medical services for themselves and their families when they get sick. But it is worth bearing in mind that there is a kind of great tribute to medicine in the push for national health insurance. It is a kind of statement that this is one of the most desired objects in life, and that in a democratic society everybody should have access to it.

Now, those who feel that way tend to think that ability to pay is an unacceptable way to ration medical care in a democratic society. If that's the case, why not an extended Medicaid program, or something of that sort? Let the government take care of the poor, and let other people take care of themselves.

That option will no doubt get serious consideration. But there is an argument against it, partly ethical and partly political.

It is not only poor people who are concerned about their ability to buy care. Nobody wants to use up his resources as the price of becoming eligible for a plan based on a test of means. The perceived need is for insurance protection before one goes broke. Most people are quite reluctant to depend on means-tested programs such as Medicaid for other reasons. Very often such programs become second-class care.

For example, less than half the physicians in the country will take Medicaid patients now because, to save money, Medicaid pays less than the going rate for services.

If everyone needs insurance, or if it would be desirable for everyone to have insurance, why isn't private insurance enough? Why is any government component needed? After all, private insurance is much more widespread than it used to be. It's true government has had a hand in that by giving tax credits to help matters along, but, nevertheless, private insurance has spread very widely, and group insurance, usually automatically accompanying employment, can do a good job.

But the protection is only as good as the industry can afford. There is very little pooling of risks from one employed population to another, so that an industry that's booming doesn't tend to pool its risks with an industry that's in a much weaker condition, and the predictable result is that many millions have little if any medical insurance coverage where they work.

Moreover, group coverage tied to place of employment has certain inherent weaknesses. It's not suited to the self-employed, to household employees, to farm workers, and to people who are outside the labor force, like widowed mothers staying home to care for young children. Continuity of coverage is a problem, as it involves unemployment, retirement, and disability. So there are a set of problems that make it not so simple as it looks at first glance, in respect to group insurance.

With respect to individual policies, they are much more expensive to sell and administer, and there are problems there too. So these are arguments to the effect that only a national plan of some kind can make sure that the population as a whole is covered by adequate health insurance.

Data collection and analysis at DHEW indicate gaps in health status, despite the improvements of recent years, which I think nobody can seriously doubt—that there have been great improvements both in the availability of care and in actual health status of the American population on a number of indices. Nevertheless, there are areas in the population, segments of the population, that suffer excessively from premature death and preventable disability. This is especially true among minority groups and persons living in inner-city or rural areas. For example, the infant mortality rates are about 50% higher in urban poverty areas than in the nation as a whole. Nationally, the U.S. ranks fifteenth in infant mortality. We are nineteenth in life expectancy for men, and ninth for women, although both those measures have been improving, and it's heartening to see that happening.

But if you take the typical American attitude that we ought to be first in health as in other matters, then it is worrisome, and, of course, there are marked differentials within the population, as Dr. Sabiston pointed out. Our statistics are pulled down very much by the poor and the inner-city and the rural populations.

How many people have no coverage at all? The HEW figures indicate that 18 million Americans have no coverage at all. The lowest figure I've seen on that is 8 million. So let's say that somewhere between 8 and 18 million have no coverage at all, and somewhere in the range of 40–50 million probably have very limited coverage, as far as one can tell from present data. So there's a lot more coverage than there used to be, but it still is pretty thin for a lot of people.

If you want to try to fix what needs fixing, without tearing down the whole house, how can you go about it? Very good minds in different fields of medicine, public health, economics, and public administration have been struggling with these exceedingly difficult problems.

We have had within this controversial field a number of approaches over the years. Some of them have been very broad, and some of them have been sharply focused, but all share the objective of seeing that everyone, within reason, has good medical care at a price that can be afforded. There are different ways you could do that, and we are not a doctrinaire, rigid society; we tend to be inventive socially as well as technically. So a lot of ingenuity has gone into recent formulations.

There have been schemes for direct government-financed and direct government-controlled plans like Medicare extended. There have been suggestions that mandate benefits through private insurance, *e.g.*, at the place of employment. And there have been suggestions for a universal government plan, but with options for employers and individuals who elect out of the plan.

In order to avoid second-class citizenship, many people prefer to meet as much as possible the need of low income people through the same plan that covers others, to try to find some way to fold the poorer people into the same plan, but with some kind of government help. There are those who feel that the extensive experience with Medicare—not Medicaid—could be built upon in designing that part of a universal health insurance plan that is to be operated by the government.

Let me say a word about the current proposals. They will be debated and analyzed and will evolve over the next couple of years.

One is the quasi-public corporation scheme. The quasi-public corporation would be created to administer national health insurance. The corporation would be responsible for enrolling all eligible persons in the plan, for establishing reimbursement policies for providers, for determining the conditions under which individual and professional providers participate in the program, and for coordinating national health resource development policy. It would be authorized to receive public appropriations and private premium contributions; private payments into the corporation would not be reflected in the consolidated federal budget. A single corporation with an independent board would be responsible for providing basic health insurance coverage to all U.S. residents.

This quasi-public corporation largely adopts the old labor-supported health security bill, but administers it through a nongovernmental corporation, in order to keep the cost and the administration out of the public sector. The other major change from the health security bill is that it requires employers to pay premiums for their workers, rather than a payroll tax. It might be considered as CHIP with a public sector bias, because the heart of the CHIP plan was to require employers to buy insurance for their employees.

The second plan I want to mention, which is in some ways quite original, was developed by Alain Enthoven, with whom I have had the pleasure of working both at Stanford and in the Institute of Medicine. It does not fit standard ideologies. It was written up in the *New England Journal of Medicine* recently.

It is based on a competitive, free market concept of health care financing and delivery. It would provide protection against major health expenses. It is called the "consumer choice health plan;" it aims to provide protection against major health expenses, and yet leave the consumer personally liable for a portion of the expected health costs. This is intended to motivate consumers for comparison shopping among a network of health care providers for a health insurance program.

Enthoven is particularly interested in encouraging HMOs, because he thinks they are more cost-effective, but in any event, his argument is that people should shop on the basis of cost, and that the more efficient providers would win out in the long run.

He sees the market pressures on providers as being very important. He would repeal many of the federal and state regulatory programs in order to diminish government intervention. He thinks that most regulations tend to increase costs and decrease efficiency and flexibility. He would try to find ways to increase consumer awareness and get more local decision-making on such matters as hospital construction and other factors that add to costs.

In many ways, his plan is modeled on the federal employees' health benefits program where there is a choice between health insurance plans or HMOs, if they are available, and a minimum benefit package, and a limit on consumer out-of-pocket liability.

Consumers would be permitted to choose annually among the plans offered in their area, and their enrollment would be subsidized through individual tax credits, or vouchers. The availability of vouchers would be an important component of the plan.

So he has influenced most of the thinking on national health insurance during the past year. His emphasis on competition and consumer choice and incentives for greater efficiency, particularly in regard to organized settings of one kind or another, has become very influential.

There is something called the target plan which I'll mention next. This is essentially the Long-Ribicoff catastrophic proposal which federalizes Medicaid, offers all Americans catastrophic insurance, and establishes a sort of "Good Housekeeping Seal of Approval" for insurance companies that comply with federal regulations. It also adds preventive benefits for children. So it's a kind of catastrophic plus kiddie-care plan.

Then there's another plan with some new elements—called the publicly-guaranteed health protection plan. It, essentially, relies on mandated coverage of all employees and the notion of enrolling all Americans in a public plan, but allowing individuals or groups to opt out into private plans. This might well result in most people who are self-supporting or who have good employment to move their premiums and insurance costs off the federal budget, while leaving everyone else in the public sector.

One of the classic problems of mandated approaches is how to keep people who aren't employed from falling through the cracks, like migratory workers, and in this plan they are automatically eligible unless they opt-out. Hence, that problem is solved in principle.

The main concern is that there would most likely be selection against the government plan, that is, companies and employees below the average risk would tend to opt-out—the best risks would probably be skimmed off, and then the public plan will be more expensive. It might be more expensive anyway, but it would get progressively more expensive as that skimming process went through a second phase and a third phase, and in ten years we might end up with the government plan having by far the greatest cost per benefit, with the lesser risks being in the private sector.

Nevertheless, there is considerable originality in this scheme, as there is in the Enthoven scheme, and it is encouraging to see original thinking in this very complex field.

Finally, there is what I'm calling a hybrid plan—it doesn't have a name yet; it's the most recent one. This plan is, in a way, a hybrid between the quasi-public corporation and the publicly guaranteed plan, but it would have a different set of relationships between federal government, state government, and the private industry. It would be a middle ground between those two prototypes; you would have stronger federal regulatory controls than the publicly guaranteed plan, but it would eliminate entirely—and this is unexpected—the direct federal operation of health insurance programs.

It would have a broader role for private health insurance companies than was envisioned in the publicly guaranteed plan, and much broader than that of the quasi-public corporation.

Two insurance consortia would be formed, one operated by the Blues and one operated by all the rest. All public insurance programs, *e.g.*, Medicare, Medicaid, would be eliminated, and beneficiaries would be enrolled in one of the two consortia plans. There would be federal funding paid to the two consortia to enroll the poor in health insurance programs. There would also be binding area budgets established by the federal government, but implemented by state governments.

Perhaps the most unique feature of this approach is the idea of the insurance consortia that would enroll the entire population of the United States, but would preserve a very large role for the private health insurance, presumably, avoid the danger of a two-class system, and would eliminate public insurance programs that were directly operated.

The consortia would administer the program, would negotiate reimbursement rates with providers; the rules and procedures, however, would be established by national and state boards.

There are three main issues of controversy about this very recently proposed plan. One is how much it would cost, and, of course, that depends partly on what kind of benefits would go into it; second, on the question of prospective budgeting, and thirdly, on the adequacy of states to administer it. If you look at the Medicaid experience, it doesn't warm your heart about the extent to which they have relevant experience to deal with it.

Now let me offer a few conjectures.

Survey research over the years indicates there is rather broad public interest in national health insurance. While it is unlikely, for a variety of social and historical reasons, that a directly owned and operated national health service will be established, even by the twenty-first century, the gradual phasing in—and I would underline "phasing," with whatever plan it is—the gradual phasing in of a national health insurance system over the next few decades seems to me to be probable.

The benefits provided will probably be narrowly defined at the outset. Some phrases like "a decent minimum" would be most apt, although reasonably adequate care in many spheres may be covered, including even modest coverage for preventive and mental health services.

In the early years of this system, my guess is that coverage will focus on curative efforts, with less on prevention, and later the preventive approach will probably become increasingly important. Protection against financial catastrophe, as Dr. Sabiston mentioned, is likely to be a part of any plan that gets adopted, although individuals will be expected to bear some significant part of the cost, perhaps in relation to personal income.

I would guess that for decades to come a mixed private and public system, rather than a monolithic, totally public system, would occur, and because of this country's history of adapting existing institutions to new functions, I would think that national health insurance will probably build on current arrangements, rather than constructing wholly new ones.

One of the concepts which will probably be a part of any national health insurance system in the long run is that coverage will apply increasingly to services which have been validated scientifically, such that benefits and risks are well documented. The cost to the nation of paying for interventions that have not been proved effective, or which have unacceptable risk-benefit ratios, will be of growing concern. Consequently, as a cost-control as well as a quality-control measure, I would think that scientific validation and assessment of interventions may be required in an early phase of their dissemination.

That will be, in the long run, a very important task for professional leadership. We must learn how to do this without stifling the innovation essential to future progress, without squashing the art of medicine, without undue constraints on talented clinicians, and without regulatory overkill.

Here I feel that the professional societies, and perhaps especially the surgical societies, because of the profound responsibility that surgeons carry in this world, can provide a great deal of leadership in terms of health care research. I believe we have built a marvelous basic science establishment in this country, and we have got to preserve that. And we have to be concerned in health sciences not only with deepening the base of fundamental knowledge, but with continuous monitoring of these advances for applications that are promising in regard to clinical problems. Moreover, arrangements are needed to ensure that there will be feedback loops from the clinical, practicing community that can stimulate the research enterprise. I think we have to broaden the spectrum of health sciences; the entire continuum of high-quality research from basic science to clinical investigation to health services research should be fostered by any comprehensive national health policy, with or without national health insurance. I don't know whether there will be national health insurance or not. However that comes out, I think one of the best results in the long run could be the stimulus to us in the medical profession to clarify increasingly the benefits, the risks, and the costs of what we do. There will always be a large element of art in medicine, but I think over the next several decades we can extend considerably the extent to which our profession rests on a science base. And that emphasis on health care research *per se* seems to be an important and constructive development.

If there is national health insurance, it might well be a good investment to take some small percentage—perhaps one per cent—off the top for health care research, especially clinical trials.

Another possibility is to cooperate with other countries in clinical investigations. Some of the costs of clinical trials, whether it be for procedures, or medications, or even modes of organization, could be shared by studying one problem in one country and another problem in another country, *i.e.*, a pooling of intellectual, technical, clinical, and financial resources for health care research. In fostering health care research, we can provide professional leadership for the continuing improvement of medicine, whether or not we have a national health insurance plan.

Prospectives of the Purchasers of National Health Insurance

MR. WILLIS B. GOLDBECK‡: The economic involvement of major industry in health care, by definition, gives persons involved in industry the right and, I would suggest, the obligation to become intimately involved in health policy. Basically, that's an obligation they have failed to meet in the past.

Most of industry has been a passive purchaser of health care and has done little to investigate what comes as a result of their purchase power, whether it is good for the employee, for the nation or for health, let alone for the company.

I think that our group and the individual corporate involvement which some physicians find disturbing shows, if nothing else, recognition that the time of being passive purchasers has come to a screeching halt. All one has to do is look at the checks signed by individual firms; some last year exceeded a billion dollars in health insurance premiums for one company for one year. It can easily be seen why those who at least would call themselves good managers and good business people can ill afford to feel comfortable about continuing to make payments of that magnitude without investigating the value received.

So, in effect, industry has become a bit of a new boy on the block in the health policy arena; while this is disturbing to some, we think it is a healthy development.

If one does not become overly concerned with the word "insurance," and if one looks at what we have in this country, he will see that we have the basic ingredients of a national health program today. We are not talking about developing some strange new thing that starts from scratch. We already have Medicaid and Medicare; a national health planning program; specific treatments, such as the renal program that are clearly national disease insurance programs; various specified subpopulation programs, such as Indians and migrants; manpower legislation that pays for a significant portion of all health education in the United States and is now increasingly involved with the locational decisions of where physicians and other providers will practice. One need only look at the number of health facilities in the United States that are tax financed; the amount of research that is tax financed; the PSRO program; the fact that the federal government is sponsoring alternative delivery systems; to know that we are part of an overall system that is intimately involved with the federal government today. You could probably make the case that we have already a national system.

The question is whether that system is working adequately. If the answer is no, it is not working adequately, although the reasons and the perceptions would vary, the next questions are: what is going to happen in the next few years to correct what is wrong with the system, and do those corrections imply major new additions to the system?

From our standpoint, trying to make business a credibly involved element of the policy debate, it is important that we appreciate that there is no single cause of today's health care problems. The providers clearly are not the cause per se, nor is the government the only bad guy. It does all of us ill to just point the finger at the government and say: If they'd just go away, we could go back to business as usual and deliver health care peacefully in the United States.

Before the government got involved, we delivered health care peacefully to some, not at all to others and very little to still others. Some government involvement has been extraordinarily beneficial.

Many have found that their research would not have gone on without government involvement.

There is about $66 billion of government involvement today, and I don't think many of us want to see $66 billion of our taxes not be well managed. It is not appropriate—at least, from our perspective—simply to say to the government: Toss that money out there, and watch what happens to it, but don't issue any rules and regulations.

There have been some positive results in health care as a result of government involvement. Certainly there is a relationship between the advent of Medicare and Medicaid and the increase in visits to physician by the poor and the drop in maternal and child mortality that has occurred since 1965 in those subsegments of the population. That is not pure coincidence.

It is particularly important that out of all of this government involvement we at the same time recognize the almost inordinate capacity of the government not to manage that money well. The migrant program is an example.

The National Health Insurance Advisory Committee, this summer, visited outside of San Antonio and found 450,000 migrants with virtually no medical care. All sorts of reasons were given for this with the federal government blaming the states and vice versa. The rather disturbing statistic is that the life expectancy of the workers is 49 years; the life expectancy for the rest of the population is 73 years. This is an employed population; they are not an illegal alien group.

That investigation was made in the summer of 1977. It was a defined population, yet nothing was done subsequently, either publicly or privately to ameliorate a definable and resolvable problem.

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There are, without even considering the giant programs like Medicaid and Medicare, more than enough examples of the problems that exist with government programs.

In looking ahead, it is important to recognize that national health insurance is not a poverty issue. Despite the fact that one of its primary objectives, both pragmatically and rhetorically is to fill gaps; nontheless, those gaps have been there for decades, and those gaps have generally been larger in the past than they are today. Most of the people represented by those gaps do not have the political leverage to produce a national health insurance program.

National health insurance and medical care costs and overall concern with health care in the United States is becoming a middle class issue; that makes it politically viable. Whether or not one feels the perceptions of a health crisis are correct, or the directions of Congress and the Administration are correct, one cannot ignore the reality that, once an issue of this magnitude becomes a middle class issue, with the resulting mail to Congress, it is no longer an issue that can be ignored.

It is essential to look at national health insurance from a broad perspective, economically and, indeed, internationally. We are in an era of limited resources that affect every segment of our economy, and we can no longer look, politically in the Congress, in regulatory administration or even privately, at health care as some distinctly separable thing that we regulate or buy or sell, apart from what else happens in the national economy. There will be no more federal budgets for health care without considerations of where that money is coming from. Therefore, we must ask, to what other social programs is the money now going?

This is reflected in the fact that the largest single call upon the government for the federalization of Welfare and Medicaid—clearly, a health policy issue—came from the White House Conference on Balanced National Growth and Economic Development. Held on February 2 of this year, it was a conference in which virtually no health care personnel were involved. The call for the federalization of Medicaid came from local governmental officials, from county and state officials and to a distinct degree from major corporate spokespersons who were at that Conference. One begins to see that the health issues are now infused into other broad policy issues, and, in fact, the future of health care may very well be determined by nonhealth factors.

Dr. Sabiston spoke of the relationship between hospital cost containment and urban policy. Unfortunately, the persons who would be put out of work most promptly by the hospital cost containment program are the persons who were focused upon in the urban policy message as those for whom we must provide more employment. I suggest to you that both policy efforts are perfectly responsible in their own right. The step that needs to be taken is the integration of those two policies.

All of this relates to the issue of rationing. It is important that Dr. Hamburg mentioned that we do have a system of rationing by income and have had one for a long time. Rationing is not a word that should scare us. We ration in the federal government. If we decide to provide ten times as much money for cancer programs as we do for cardiovascular programs, despite the fact that we know that many more people will suffer from cardiovascular illnesses than will suffer from cancer, we are rationing care; we're determining that certain people will die of certain illnesses. That is not an evil; it's a simple political and economic reality.

Industry rations health care all the time. "Industry" is used in the sense of the amalgum of management and labor. If companies negotiate a plan that provides for dental care and does not provide for vision care, within six months the employees teeth will receive better care than their eyes. They will seek care which is ostensibly "free." The physicians will follow, perfectly responsibly and reasonably, the economic incentives of the system in which they are working.

One of the negative impacts of the plethora of private insurance programs is that they have emphasized, in many cases, the wrong kinds of care. They have relied upon throwing the money out upon the physicians, the providers and the hospitals and telling them to manage it in a cost-effective way.

When the reports came back showing that maybe the money wasn't managed as the purchasers decided would be appropriate, they began to squawk about the physicians' behavior. It seems to me that, if the industry and labor wish to complain about how the economics of the health care system work and what the results are, those segments of the society that are purchasing the care should change the incentives. Then, the provider behavior will change accordingly.

Industry must do a great many things changing its own benefit designs, programs and policies to focus upon prevention, to focus upon education, to focus upon out-patient care and to make the economic incentives lead providers toward the directions which may preclude the need for national health insurance.

It is certainly true that a lot of the stimulus for all of this comes under the general guise of a concern for cost, or a cost crisis. I don't know whether it is a crisis or not. If it is, it is a self-induced crisis, which occurred because we demanded things of the medical profession that could not be provided. Patients demanded that physicians take care of them for those things which they visited upon themselves with great regularity. If they stopped doing it to themselves there would be less for physicians to do but health care costs would be lower and the population healthier.

Nobody knows what the right amount of cost is. Nobody knows what the right health budget is for this country. Clearly, nobody knows whether 8.6%, or 8.9% or 9.1% of the gross national product is right or wrong. If anybody knew it, he would come forward, and we might even believe him. I don't think anybody knows in any other country either. It's one thing to set a number; it's certainly another to know whether it's the right number.

I'm not particularly interested in the potentiality of national health insurance to set a leveling on the health component of the GNP. If the public decided that the health care field is king, and as a major employer warrants having a larger increase in the GNP, regardless of health outcome, so be it. That may be perfectly appropriate. However, the economic implications of that for the other sectors of society and the implications for the other social objectives of society should be understood.

What this comes down to—and this is absolutely essential for assessing the impact of any kind of national health insurance—are changing values in society. The whole issue of the environment versus health versus productivity is a value issue, and it is being fought on a whole variety of fronts right now. I mentioned cost containment versus employment; there are a number of others.

If, in fact, cost-containment is to be realized in the United States, we have to reexamine our values vis-a-vis antitrust. It is absolutely incredible to have one agency of the federal government saying, "By all means get together, hospitals, manage your resources better, share your services," and right down the block another agency is suing you for doing it. It just doesn't make sense.

Again, that is a question of values, and neither agency is wrong. Both are meeting their mandated positions. They're not wrong. They're doing right. It's up to the public to indicate which value we want to follow, because the other value has got to change. They are competing values.

The same thing applies in the whole area of the public's perception of medicine and its production of health. Dr. Sabiston mentioned this. It is essential to understand that more does not necessarily mean better in the health care field. It will in certain instances, but no longer can quantity of care be automatically equated with better outcomes.

It is important for industries to understand this, because the general thrust of the corporate programs has just been to give more, not worry about the outcome, and to assume the outcome would be better for everybody concerned. This is not always true.

Connected with this are a whole series of myths that are changing, not the least of which is that involvement of industry must indicate that in some way or another industry wants to take over the health care system. I can assure you, I have yet to find a chief executive officer who wants to become a doctor or practice surgery. Most are quite content with their own large salaries and the world in which they have succeeded. They have no interest in getting into your world directly, but they do see a direct correlation between the money they pay to health care providers, and their own corporate and societal responsibilities. I would suggest that this is an appropriate relationship, an appropriate concern and one which will ultimately advance the cause of health care delivery.

The consumer is no longer to be considered too dumb to understand anything about his or her body or self. That has been a basic assumption, and it's an assumption that is rapidly changing. It needs to keep changing.

"Planning is unconstitutional." That was on my list of myths a couple of weeks ago. Happily, it is no longer on the list, because the Supreme Court has determined that planning is not unconstitutional, nor is the federal government's managing of monies at the local level.

The last myth is that, by a national health insurance program, or by physicians changing their behavior overnight or by the public's changing life styles overnight—there is going to be some quick reversal in the trends in health care and the cost of health care. This is not so. There will be no quick fix, and there will be no cheap fix. We are going to pay for whatever changes we want in the process of delivering health care in the United States today.

Before looking ahead at national health insurance, it is important to recognize that I do not speak for all business. The Washington Business Group on Health deals with large firms, for example, 27 of the first 30 of the Fortune 500, I cannot speak for small business. I have a small business, and many of the things I have to contend with for my constituents in this job would be diametrically opposed to what I might need in my own corporate setting.

Business is not in any way trying to suggest that it is "the answer." In our assignments in the WBGH, we're looking at national health insurance from the standpoint of: If it comes, what can we do to make the substance of national health insurance better? We are not starting from the premise of whether there should or should not be national health insurance.

Certain deductions can be made from the plans that Dr. Hamburg outlined. In the last year it has been determined that there probably will not be payroll tax financing. Clearly, we are pleased with that. There probably will be some kind of a mandated minimum benefit package. There will indeed be a carved-out place for health maintenance organizations or prepaid group practice and other organizational settings. That is almost 100% certain now. There is a trend toward fee scheduling. Private insurance will exist, certainly much more regulated than it is today, no matter which plan is adopted. The opt-out concept probably will be allowed, regardless of which plan is adopted or whether it's called the publicly guaranteed plan.

That may not represent a philosophical change, but a practical one. We can start with an opt-out and take care of a segment of the population that way. If the system either doesn't work or if we, over time, wish to fold them in, we can do so. Why create an enemy out of the covered segment of the population right at the outset by trying to pass national health insurance as a whole?

There will be some form of tax credits related to the small business problem. There certainly will be a phased-in program. I suspect that there will be an increasing effort to have some method of assessments for medical technology; I don't just mean hardware. Catastrophic coverage will most likely be an early, if not the first phase. The concept of packaging catastrophic coverage with child care is an appealing political package that should not be ignored.

One of the tough issues is whether or not mental health benefits are going to be included. This is a personal concern of mine and increasingly so of industry. At present we are looking at a number of experiments around the country, in a variety of settings, that seem to show an exciting relationship between provision of a controlled mental health benefit and reduction in the utilization or hospital/medical/surgical benefits. These are exciting preliminary results. One program in California shows a reduction of more than 20%.

There are several corporations that are doing serious cost-benefit studies of their mental health programs for the first time. One of the largest in the country will be released in July 1978. That looks as though the entire mental health program will pay for itself completely by reduced absenteeism alone. We're doing a case study book on a variety of these that will come out later in the year.

The message for the designers of national health insurance is certainly clear: they must look at mental health quite differently than they have in the past.

We have a common interest. The "we" is not only the providers and industry. It is also the government. The government is a purchaser, a provider, and a consumer. The government faces the same set of competing influences that we do, and that many of you do.

More importantly, there is no separate pot of money. There is no such thing as federal money or corporate money. There is only our money. What happens to our money in national health insurance, whether it is a finely articulated program or has many in-place and to-be-added elements, will depend on the will and the strength of the leadership that can be articulated by, among others, you. It's an exciting period. Industry has a great stake, and a great stake in working with you.

Who Should Be Covered by National Health Insurance?

DR. THEODORE COOPER§: National health insurance is an important topic and is of great general interest. You can say something good about it, and you can say something bad about it. You can make predictions with a straight face, about all sorts of things—dates, forms, expenditures—all based on numbers and, therefore, obviously highly scientific. You can use a fashionable jargon to reflect your expertise. You can use names of proposals and refer to one of their thinkers—or was it their tinkers?—by his or her first name, by mistake, of course. In short, it's great speech material, and you never need to fear that anyone will expect anything you say to be taken too seriously.

Yet it's rather important that we do understand something of the issues, for under this rubric of national health insurance one indeed could include a staggering requirement for restructuring the way we deliver services to the sick.

Indeed, a good deal of what is being "discussed" right now in Washington, as you have heard, amounts to a substantial, ideological, philosophical—if you wish—revision of the concept of the health professions—but principally physicians. The great traditional professions—for the moment I'll exclude the oldest for the purpose of this discussion, although I'm not sure I should be, by current rhetoric—I meant law, medicine, and theology—were presumed to accept the responsibility for others as part of their societal standing and their delegations from society. And yet today we are not trusted to be concerned with others. The federal government seems to think that only through its good offices can one ensure that we can be and will remain to be responsible for others. And the decline in that confidence by the government is proportional to the increase in expenditures in the system.

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The health insurance system, not surprisingly, has failed to distinguish between needs and wants. In a society whose standard of living continues to increase, the rate of conversion of wants to needs is rapid. The cycle length between distinguishable points of change and public aspiration and expectation is becoming shorter, and that is why it is so fashionable, and yet so difficult, to identify what Bill Goldbeck just called gaps, as part of the rhetoric about national health insurance.

The implication is, therefore, that for all practical purposes a health insurance system should provide financial coverage for what the person feels is required for his or her appropriate health care. Thus, contrary to much common gossip, the public really becomes the governor on the system—the primary governor—not the physician. That is not to say, however, that the doctor is not a factor in the rate of expenditures in the system.

Of course, the physician is the large determiner of what is done for an individual patient. It is not only true; it happens to be appropriate. Of course, I understand that it may take two doctors or more to give an honest or informed opinion for surgery. If that is so, then I think you surgeons out there better intensify your educational programs, or at the very least you should give a course on how to render a productive second opinion.

What has happened with an interesting, not-too-well-thought-out investigative technique, that thing called second opinion, is an important lesson. A purported research tool is being introduced as a standard of practice, even to the point of implying that it is the preferred approach to judgments of quality, or the preferred approach to an intimate process of decision-making that has traditionally occurred between the physician and patient.

It has often been claimed that too many people go to the doctor for imagined illnesses rather than real sickness. Should we allow payment for these worried well people in our insurance scheme, or should we, as John Burnham recently wrote, deal with these people in a proper and humane way as physicians?

I suppose an expert economist or a committee in Washington could, indeed, devise a form which could be reviewed by another committee, and a staff, of couse, and then the Inspector General, to make sure that there is not unnecessary medical practice. At the same time, the same department will be urging everyone to go to their doctor, or to an HMO clinic, or to some other health professional to get everything detected at the earliest possible stage, perhaps when it is only a chemical marker in asymptomatic people, or a spot on some modern, high-resolution radioelectronic equipment; equate the expenditure there to a misuse of technology.

Physicians are best advised to decide in a way that saves money. But how to do this without charging for it is a real challenge. In addition, the challenge is how to do it, without missing anything.

Defensive medicine will continue to grow, with increasing public expectation of early detection or prevention. Therefore, this nation had better get on with distinguishing between real negligence and social compensation. It is an area apt to be neglected in the debates on national health insurance.

Insurance, one would think, ought to be available as a mechanism for people who want to provide surety of resources for health care. If one chooses not to invest in this mechanism, what should be his or her *risk*? Well, he or she could either be able to pay for it from his or her own resources, or, wanting resources, he or she forfeits the ability to make the choice that the financial security of insurance and the physical availability of services would provide. This does not mean that the person would forfeit access to care. It means that there would be great restriction of choice. It would not imply inferiority in the technical sense, but to some it would imply inferiority in the social sense of what medical care in 1978 should be: comprehensive sociomedical care.

This is what I consider the fundamental philosophic issue of the insurance choice. Should the national program be voluntary or mandatory? If it is mandatory, then there is a question about who should have it. Everyone *should* have it. The debate becomes one of how to finance it; how to regulate it.

Some folks would equate mandatory with equal. The equal implications of the political rhetoric will be the fundamental linchpin of proponents of national health insurance. A common way of saying "equal" at this time is "one-class medicine."

It is, of course, 180° out of phase with efforts of cost containment. We continue to sell the concept in this country of always having the best possible for every person, much less every patient, while we continue to urge everyone to spend less. There is some notion that if you change what you do—that is, less testing, use less technology—you could still do the best for everybody, providing you didn't charge so much.

But the way to do more and spend less, to do it for less money, is to devalue your services, or to do it at a lower level of something. The likelihood of a direct devaluation of services or goods in the health sector is remote, without similar devaluation in the rest of the economy, even though this, in effect, is what most people would like to happen.

Therefore, if one spends less, one could look forward to lesser services and lesser goods. Thus, it bears out the dictum that the drive toward parity—equal concepts—will seek a lower common denominator of equality at prevailing or increased costs.

In the face of an expanded insurance program, prevailing costs would not hold. It is quite likely that market theory in this case would apply to medicine, and would be quite predictable. Therefore, if the program is to be voluntary, we need to clarify the means necessary to prevent the financial barrier from excluding the participation of the poor. And, one could even properly ask if the wealthy should be allowed to participate in the same way. And this is not to say that the wealthy should be denied care or insurance by the government.

To some, these questions might seem farfetched, but they are actually talked about in the Enthoven plan and several of the others that have been mentioned this morning. We think they are farfetched, because we are rapidly approaching the view as a people that there are no options possible except to have everyone covered the same way, and that we cannot trust anyone to make the choices except the government.

That 18 million people do not have insurance, and that 40-or-so million have inadequate coverage, is often equated with the idea that 50–60 million Americans have no health care, or at least inadequate health care; and I would submit that this is certainly not the case. Some figures were presented on blocs of people with no health care, but we're not talking about 40–50 million Americans in that category.

If one really wants to get down to it, some folks with plenty of coverage get quite inadequate care for different reasons. Furthermore, the push for uniformity is one of the reasons, why the whole Social Security System, at the moment, is creaking.

It is important to realize that the total aspiration in this country for health services, as has been pointed out by other speakers, will not be achieved by simply removing the financial barriers alone, and it will require a broad policy in health; and by that I do not restrict it to a broad policy in cost containment either. Certainly, I believe that we are in need of restraining many things in the system, including the rate of escalation of our expenditures, and this should not become the fulcrum for the entire discussion about judgments and choices to be made in lowering financial barriers.

There is another way to respond to the question of who should have insurance. And that would be to say that anyone who would become a financial cripple as a result of paying for health services should be protected from that fate. Hence, the concept that you heard about of catastrophic insurance as a current need of a first-phase program. There is substantial public sentiment, as you have heard, for this type of protection. In actuality, that number of people on a percentage basis is a very small one. There is substantial public sentiment for a second phase, of a federalization of Medicare–Medicaid, because it is a poor program, as perceived by almost everyone.

The number of people involved here has been alluded to. We are talking about, probably, a few million on the catastrophic, $25 million on the federalization of Medicaid. In any case, the decision on that is not really a medical issue. It becomes a public policy issue, and even the small portion of Phase 1 will be inflationary. It could remove incentive for prompt deinstitutionalization. It might foster costly, heroic efforts. It will precipitate a cyclic reevaluation of what is a catastrophe. And the method of financing may become a very important model for financing the entire system.

I think those arguments have been pointed out many times in the past, but it is probably clear that the sentiment for filling this gap, or providing additional protection for those in that situation, will be the first phase of a new insurance expansion.

It should be clear, however, that even the gap-filling, or need-filling will not ensure the best, or the concept of equal. However, it will assure that the public aspiration for the best and the public aspiration for the same will be filled, particularly by catastrophic coverage, for it is through this means that everyone with cancer can have the best new therapy; that everyone who needs a coronary bypass can have a coronary bypass, provided that they have access on a geographical basis to the best centers for heart surgery, cancer therapy, and so forth.

I am not opposed in principle to these types of protections, but I am not an impractical person either, and I don't think we should sit here and tilt at windmills. So I do agree that within a reasonable period of time some further expansion of the system will occur, and probably in the phases already outlined by the others.

But it seems to me, as we do this, we are clearly at cross purposes with ourselves, and certainly no program of national health insurance is politically viable that excludes anyone, ultimately, from coverage. And the question really becomes, then, not who should be covered, but, on a practical, political base, what should be covered.

People do not understand (in my opinion—most of the public does not understand) that there are to be limits on a national program of health insurance. Current practices and concepts of itemized billing tend to be inflationary, but all the discussions of this order continue to drive the notion in the public mind that what is to be covered is everything. I think many people would be greatly disillusioned to hear Bill Goldbeck point out that the most vulnerable part of the compromises being worked out is the mental health package, for, indeed, this is considered to be one of the things—and one of the reasons—why an important discussion of national health insurance is taking place again in this decade.

The promise, or at least the perception of that promise, is what draws the public, and what they think they are getting is access to everything, and the best for everyone. If that is not the case, then someone had better inform them pretty soon that there are and will be limits, and that there are and will be restrictions, and that there will be out-of-pocket costs for most people. Someone had best soon begin to tell the people that, to a great extent, the cost constraint therefore also lies in their hands.

Regulation by the government will not suffice to let everyone have it all ways. It should also be made clear that those societies who control their systems more than we do do not have it better. And they do not have it at a relatively reduced rate either, if you are to include what most people think will be covered in a national program.

Therefore, it should be clear that it is the law of the land—right now it is the law of the land—that every citizen should have access to quality care at reasonable cost. To the extent that national health insurance will help toward that objective, it needs to be pursued. Access to insurance, however, and access to care are not the same thing. What we need is clarification of policy in which insurance becomes a useful mechanism to achieve that objective, but not the only means to that objective. All citizens in this country, at this standard of living will continue to seek the best in quality care. All politicians, in the final analysis, will be sensitive to that aspiration.

How it is to be achieved in this country, along with an acceptance of limits, an acceptance that the facts are that there cannot be one quality care, that, in fact, everybody can't get the best treatment in the best place, that every community cannot have the best place that is the same as every other place, that every citizen can get care without having the same means of gaining that access—all these things must be brought to an important public discussion, before the decisions are made on who and what is to be administered in the way of national health insurance.

So I would reiterate what I said to a similar audience several months ago. It would be my hope that before a program of national health insurance is seriously debated in the Congress, that the real, substantive issues—and by that I mean what the public thinks it's getting into—are discussed properly with the public on a large scale, preferably in prime time, preferably handled by a credible nonvested interest.

What will not be tolerable, and what, indeed, is not tolerable at the moment in American planning for health programs, and national health insurance included, will be a difference in basic quality. But the difference in basic quality that is being sold as one-class medicine needs to be distinguished by what is the difference in basic social amenities. It is to a great extent the oversell of what that difference is that is one of the largely neglected areas of the total debate of national health policy. It is the one which is politically difficult to deal with. It is the real governor on the system of how to put some practical limits on a program which, basically, has the right motivation.

It is the point at which, intuitively, most physicians feel that the restriction on their activities, by trying to solve that problem through regulation, makes a program of governmentally sponsored and controlled national health insurance an unpopular future determiner of the way that we practice medicine.

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Rhoads TEXTBOOK OF SURGERY

Principles and Practice

●

Edited by JAMES D. HARDY, M.D.
with 279 contributors

Although technically a Fifth Edition of *Surgery: Principles and Practice*, this revision is new in *title, editor, contributing authors, content, approach, and format*. It has been reorganized into three major parts: General Principles of Surgical Practice; Specific Lesions and Dysfunctions Involving Various Organs; and Parasurgical Considerations.

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Percodan® ⒸII

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

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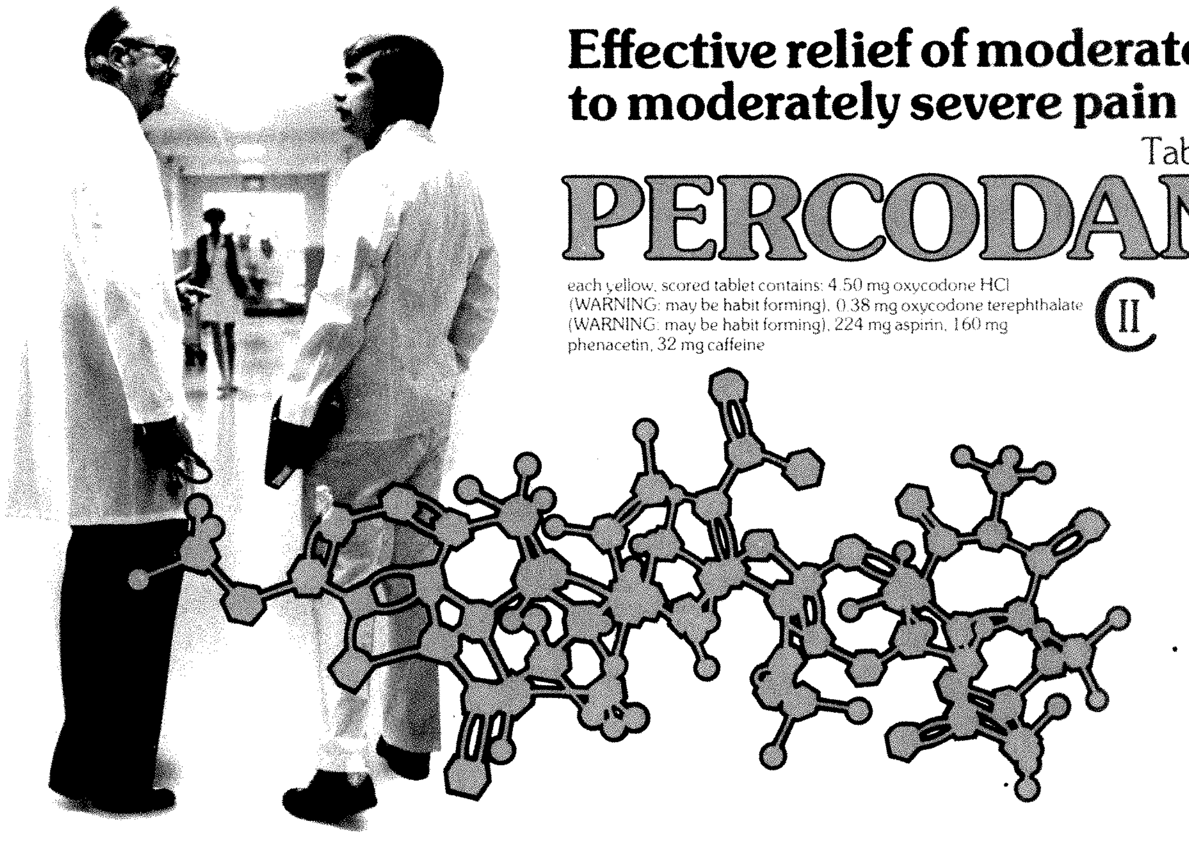

Effective relief of moderate to moderately severe pain

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Reliable and safe hemostat

to help control small-vessel bleeding without injuring vital tissue

SURGICEL

TRADEMARK

Absorbable Hemostat

(oxidized regenerated cellulose)

SURGICEL Absorbable Hemostat
TRADEMARK
(oxidized regenerated cellulose)

FOR SURGICAL USE

(For dental applications of this product, reference should be made to the package insert for dental use.)

DESCRIPTION: SURGICEL Absorbable Hemostat is a chemically-sterilized, absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and can be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance.

ACTIONS: The mechanism of action whereby SURGICEL accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors including the amount used, degree of saturation with blood, and the tissue bed.

INDICATIONS: SURGICEL Absorbable Hemostat (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective.

CONTRAINDICATIONS: Although packing or wadding sometimes is medically necessary, SURGICEL Absorbable Hemostat should not be used in this manner unless it is to be removed after hemostasis is achieved.

SURGICEL should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

When SURGICEL is used to help achieve hemostasis around the spinal cord in laminectomies, or around the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure.

SURGICEL should not be used to control hemorrhage from large arteries.

SURGICEL should not be used on *non-hemorrhagic serous oozing surfaces,* since body fluids other than whole blood, such as serum, do not react with SURGICEL to produce satisfactory hemostatic effect.

WARNINGS: SURGICEL Absorbable Hemostat is supplied sterile and should not be autoclaved because autoclaving causes physical breakdown of the product.

SURGICEL is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

Closing SURGICEL in a contaminated wound without drainage may lead to complications and should be avoided.

The hemostatic effect of SURGICEL is

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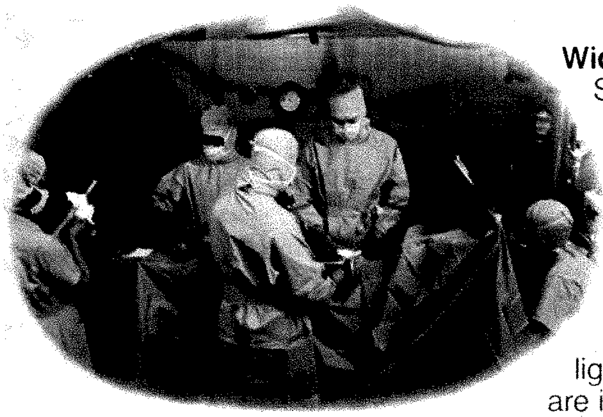
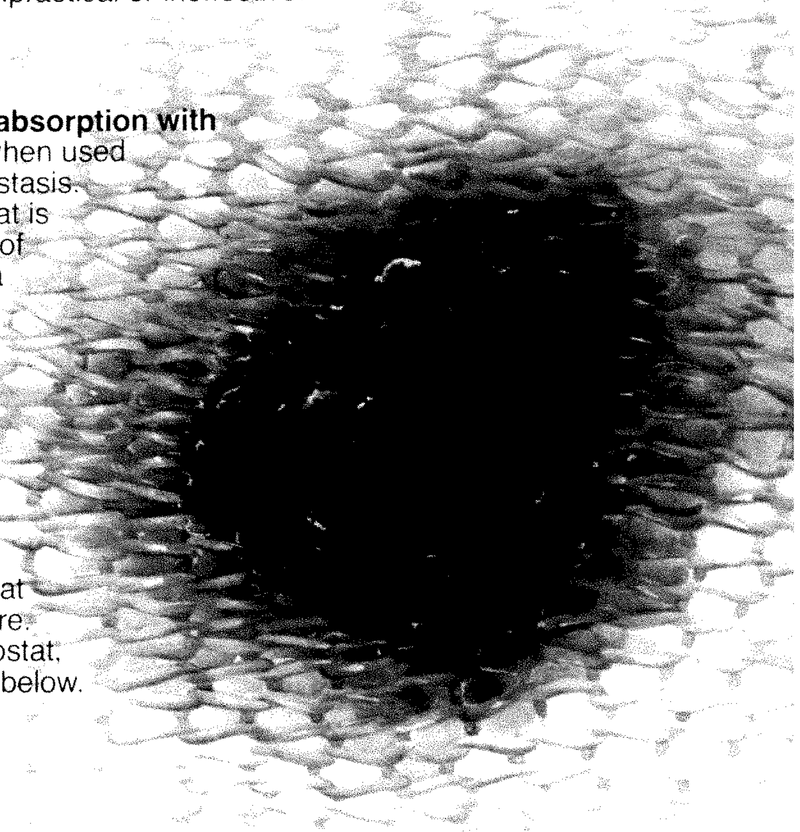


Wide hemostatic application in surgery. SURGICEL* Absorbable Hemostat is a pliable knitted fabric that has been found to be inherently and dependably hemostatic when used as an aid in the control of small-vessel bleeding in abdominal, thoracic, neurosurgical, orthopedic, cardiovascular, gynecologic and otorhinolaryngologic procedures, in superficial open wounds and on donor sites. SURGICEL Absorbable Hemostat is a valuable adjunct in the control of small-vessel bleeding when ligation or other conventional methods of control are impractical or ineffective.



Rapid and complete absorption with virtually no tissue reaction when used properly in minimal amounts for hemostasis. SURGICEL Absorbable Hemostat is completely absorbable from sites of implantation after it has become a gelatinous mass that aids in the formation of a clot.

Convenient to use. SURGICEL Absorbable Hemostat requires no additional hemostatic preparation; it is ready for use directly from the vial. When exposed to blood, it adheres readily to tissues but generally not to dry instruments or dry surgical gloves. SURGICEL Absorbable Hemostat should be stored at controlled room temperature. Before using SURGICEL Absorbable Hemostat, please refer to product information below.

greater when it is applied dry; therefore it should not be moistened with water or saline.

SURGICEL should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved. It *must* always be removed from the site of application after use in laminectomy procedures and from foramina in bone when hemostasis is obtained. This is because SURGICEL, by swelling, may cause nerve damage by pressure in a bony confine. Paralysis has been reported when used around the spinal cord, particularly in surgery for herniated intervertebral disc.

PRECAUTIONS: Use only as much SURGICEL Absorbable Hemostat as is necessary for hemostasis, holding it in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction.

SURGICEL should be applied loosely against the bleeding surface. Wadding or packing should be avoided, especially within rigid cavities, where swelling may interfere with normal function or possibily cause necrosis.

In *urological procedures,* minimal amounts of SURGICEL should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.

Since absorption of SURGICEL could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.

If SURGICEL is used temporarily to line the cavity of large open wounds, it should be placed so as not to overlap the skin edges. It should also be removed from open wounds by forceps or by irrigation with sterile water or saline solution after bleeding has stopped.

Precautions should be taken in *otorhinolaryngologic surgery* to assure that none of the material is aspirated by the patient. (Examples: controlling hemorrhage after tonsillectomy and controlling epistaxis.)

Care should be taken not to apply SURGICEL too tightly when it is used as a wrap during vascular surgery (see "ADVERSE REACTIONS" section).

ADVERSE REACTIONS: "Encapsulation" of fluid and foreign body reactions have been reported.

There have been two reports of stenotic effect when SURGICEL Absorbable Hemostat has been applied as a wrap during *vascular surgery.* Although it has not been established that the stenosis was directly related to the use of SURGICEL, it is important to be cautious and avoid applying the material tightly as a wrapping.

Possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy have been reported. There has been one report of a blocked ureter after kidney resection, in which postoperative catheterization was required.

Occasional reports of "burning" and "stinging" sensations and sneezing when SURGICEL has been used as packing in epistaxis, are believed due to the low pH of the product.

Burning has been reported when SURGICEL was applied after nasal polyp removal and after hemorrhoidectomy. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL was applied on surface wounds (varicose ulcerations, dermabrasions, and donor sites) also have been reported.

SURGIKOS

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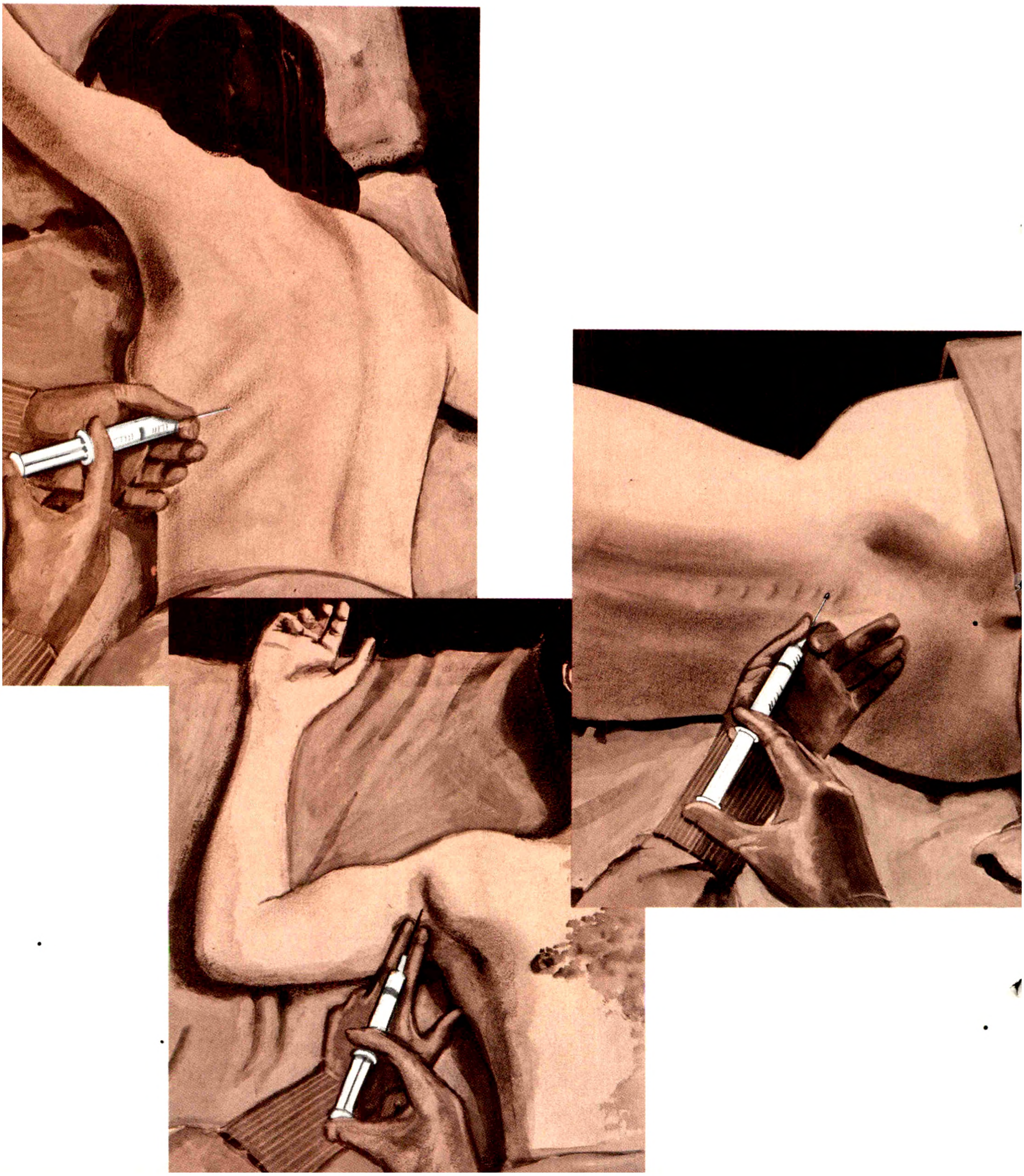
brand of
only because **bupivacaine hydrochloride**
of its prolonged action...



...you're missing three other important reasons.

1. More control of motor block

The variety of Marcaine dosage strengths and the ability of Marcaine to provide complete sensory block *with* or *without* significant motor block gives you more control during surgical procedures.[1]

2. Less need for postoperative analgesics

Marcaine with or without epinephrine has been demonstrated to postpone or reduce significantly the need for postoperative narcotics.[1,2]

Results vary with the procedure and the dose administered.

3. Greater postoperative patient mobility

Of 20 patients with flank incision, half were given intraoperative bupivacaine (Marcaine) intercostal blocks. Those who were given Marcaine required less pain medication, were sitting up 2 days earlier, walking 3 days earlier, and took a regular diet 2 days sooner.[3] Ability to cough and breathe deeply was also greater in the Marcaine patients.[3]

The local anesthetic with more reasons to use it than any other.

Marcaine® hydrochloride

brand of

bupivacaine hydrochloride

with or without
epinephrine 1:200,000

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on the next page. As with any local anesthetic, inadvertent intravascular injection may result in general convulsions.

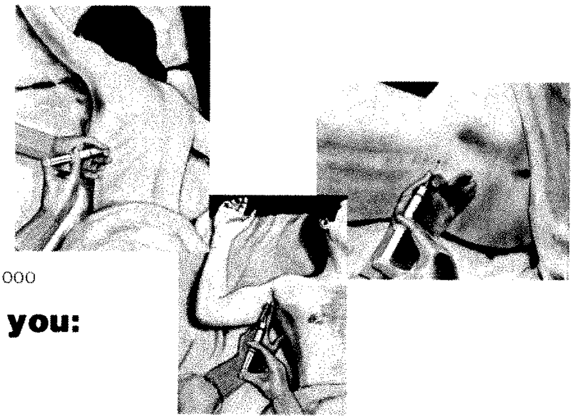
Please see following page for full prescribing information.

Marcaine® hydrochloride

brand of

bupivacaine hydrochloride

with or without
epinephrine 1:200,000



The long-acting local anesthetic that gives you:

1. **More Control of Motor Block**
2. **Less Need for Postoperative Analgesics**
3. **Greater Postoperative Patient Mobility**

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References: 1. Moore DC, Bridenbaugh LD, Thompson GE, et al: Bupivacaine: a review of 11,080 cases. *Anesth Analg* 57: 42-53, 1978. **2.** Lund PC, Cwik JC, Vallesteros F: Bupivacaine—a new, long-acting local anesthetic agent: a preliminary clinical and laboratory report. *Anesth Analg* 49:103-114, 1970. **3.** Noller DW, Gillenwater JY, Howards SS, et al: Intercostal nerve block with flank incision. *J Urol* 117: 759-761, 1977.

BREON
BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

FORMULA

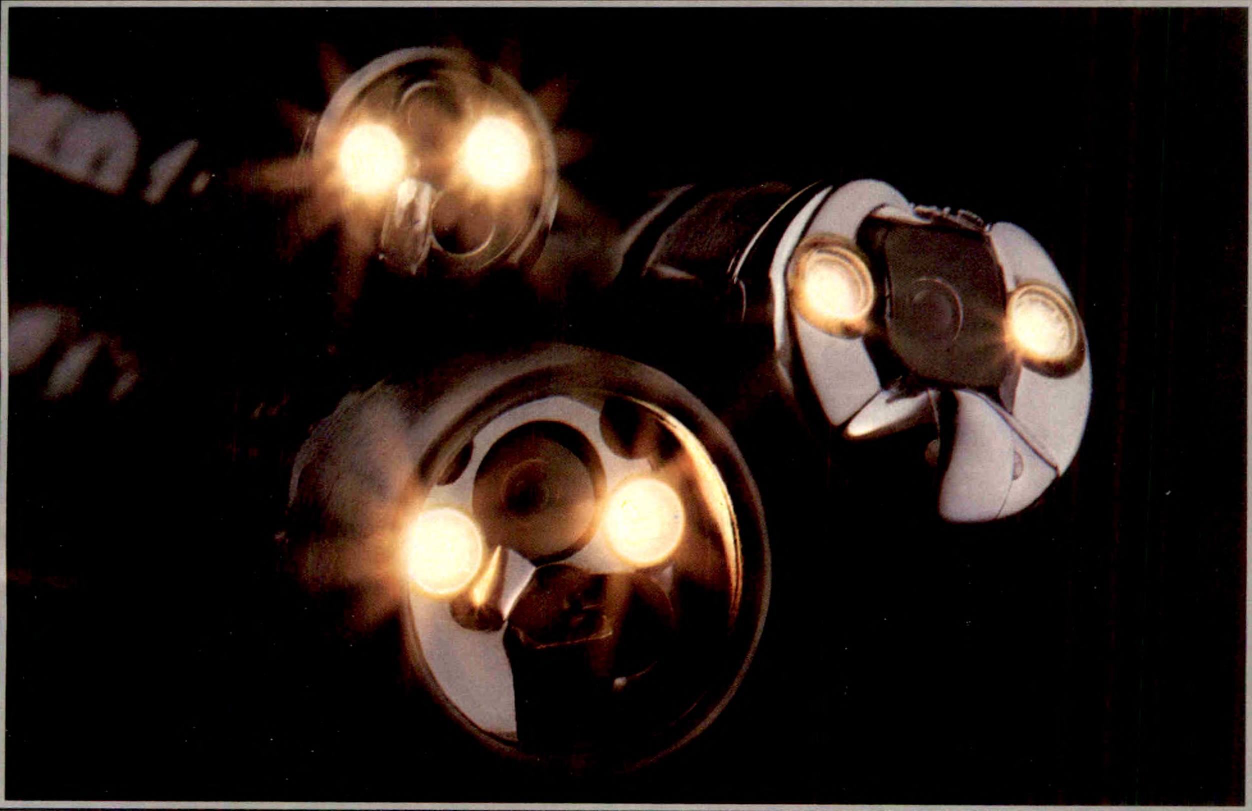
PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl) %	mg./ml.	**Epinephrine* (as bitartrate)** Dilution	Methyl-paraben mg./ml.	Sodium Bisulfite mg./ml.	Thio-glycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.	Sodium Bisulfite mg./ml.	Thio-glycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.50	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.50	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						0.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

SEE FOR YOURSELF WHY OVER 90% OF TEACHING HOSPITALS USE OLYMPUS UPPER GI FIBERSCOPES.



One look through an Olympus scope will show you: The answer is in the optics.

You can't ask for any higher endorsement than to be judged the clear choice in fiber optics by those who know, and expect most from, upper GI endoscopy. Olympus fiberscopes represent the culmination of over sixty years of precision technology in medical optics. Their optical superiority, enormous deflection capability and ease of control combine to deliver an image of unmatched clarity no matter which site of the GI tract you are examining.

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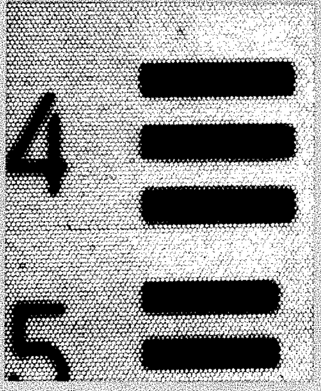
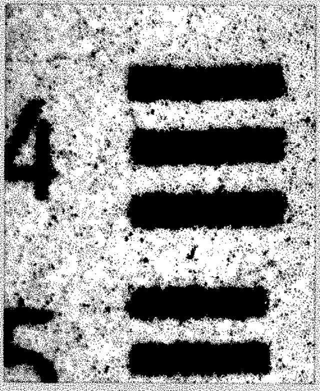
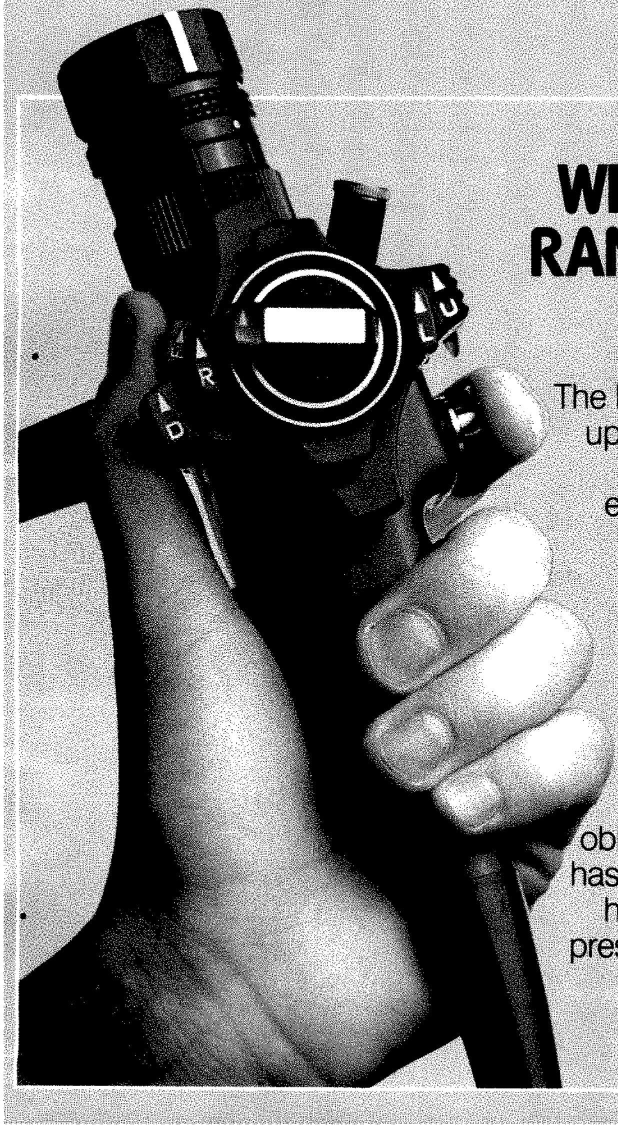


Test pattern photographed with an Olympus fiberscope.



Same test pattern through a competitor's fiberscope.



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The Olympus GIF-K is the only oblique-viewing upper GI fiberscope available. It has an enlarged, 85° field of view. All the ease of handling of end-viewing fiberscopes has been preserved, while drawing on the advantages of a side-viewing scope: the best of both worlds.

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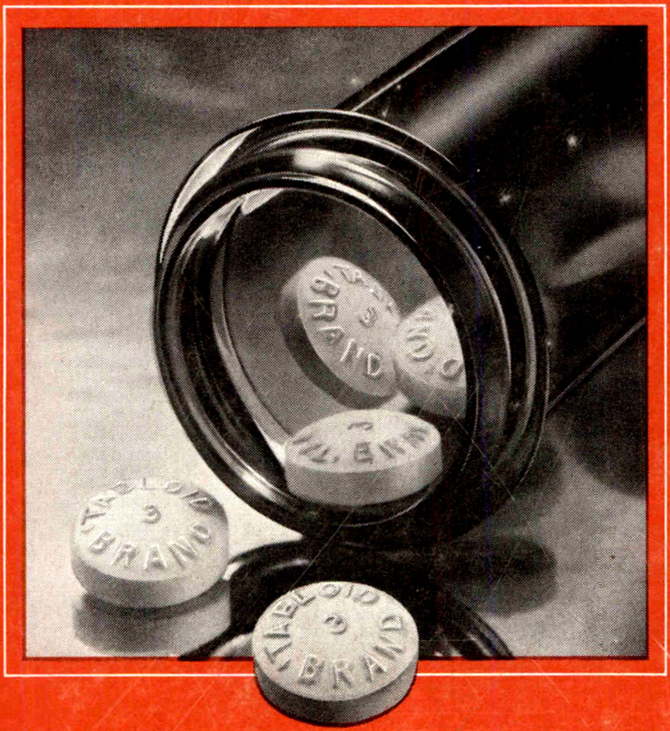

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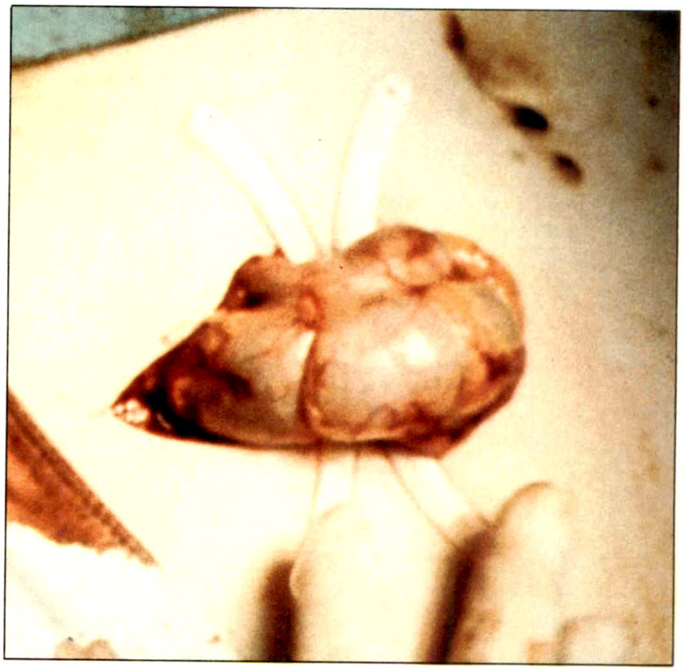

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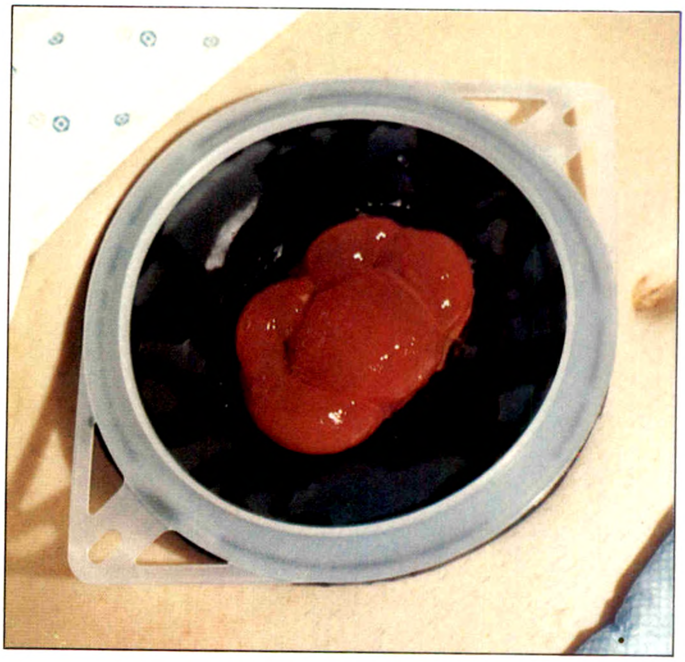

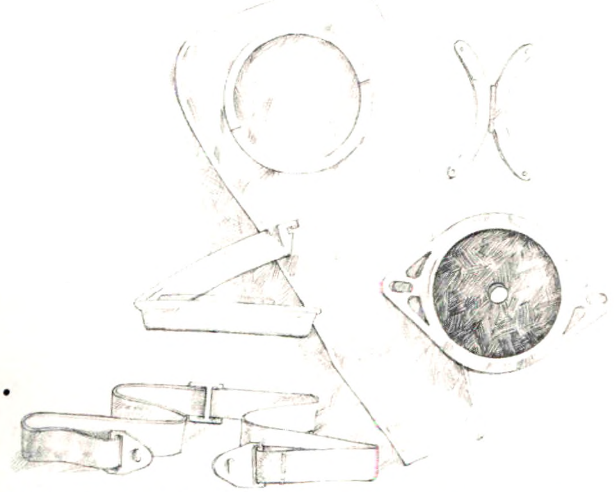

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POSTMASTER: Send address changes to Annals of Surgery, J. B. Lippincott Co.,
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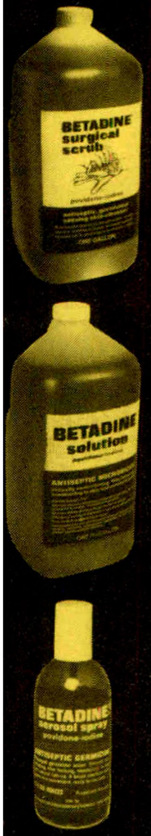

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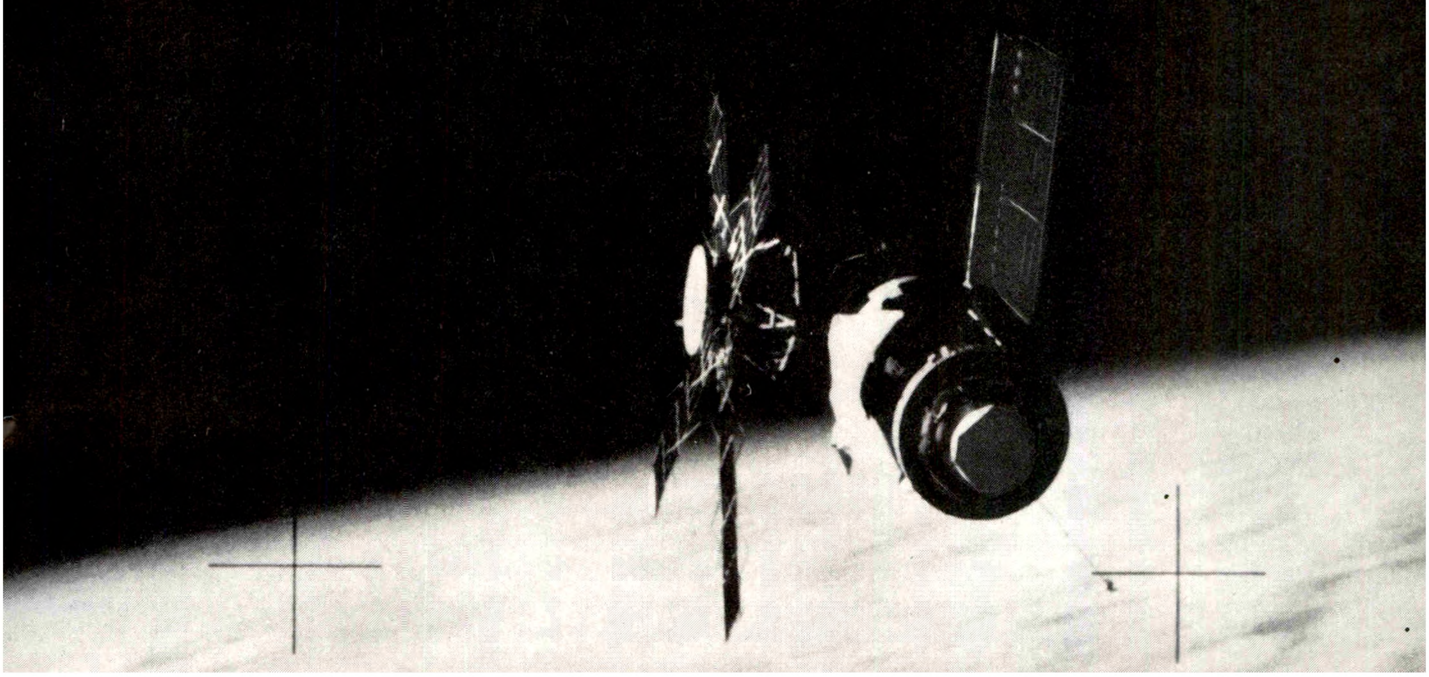

Bacteroides

may be implicated
in a number of clinical situations,
including . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena

Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffect
contraindicated.

But when bacter
cated, Chloromyc
phenicol) therapy
conservative cou
situations, the be
with Chloromyceti

See next page for
information.

Bacteroides...

often an indication for

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(chloramphenicol) Sodium Succinate

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WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

MPORTANT CONSIDERATIONS IN PRESCRIBING INECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

HLORAMPHENICOL SODIUM SUCCINATE IS INENDED FOR INTRAVENOUS USE ONLY. IT HAS EEN DEMONSTRATED TO BE INEFFECTIVE WHEN IVEN INTRAMUSCULARLY.

. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.

. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.

. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

hloramphenicol is an antibiotic that is clinically useul for, *and should be reserved for*, serious infections aused by organisms susceptible to its antimicrobial ffects when less potentially hazardous therapeutic gents are ineffective or contraindicated. Sensitivity esting is essential to determine its indicated use, but nay be performed concurrently with therapy initiated n clinical impression that one of the indicated condiions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramhenicol sodium succinate contains approximately 52 ng (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

n vitro chloramphenicol exerts mainly a bacteriostatic ffect on a wide range of gram-negative and gramositive bacteria and is active *in vitro* against rickettias, the lymphogranuloma-psittacosis group, and *Vibrio holerae*. It is particularly active against *Salmonella yphi* and *Hemophilus influenzae*. The mode of action s through interference or inhibition of protein synhesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed apidly from the intestinal tract. In controlled studies n adult volunteers using the recommended dosage of 0 mg/kg/day, a dosage of 1 g every six hours for eight oses was given. Using the microbiological assay nethod, the average peak serum level was 11.2 mcg/ml ne hour after the first dose. A cumulative effect gave peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 8-hour period. Total urinary excretion of chloramphencol in these studies ranged from a low of 68% to a igh of 99% over a three-day period. From 8% to 12% f the antibiotic excreted is in the form of free chlormphenicol; the remainder consists of microbiologcally inactive metabolites, principally the conjugate ith glucuronic acid. Since the glucuronide is excreted apidly, most chloramphenicol detected in the blood is n the microbiologically active free form. Despite the mall proportion of unchanged drug excreted in the rine, the concentration of free chloramphenicol is elatively high, amounting to several hundred mcg/ml n patients receiving divided doses of 50 mg/kg/day. mall amounts of active drug are found in bile and eces. Chloramphenicol diffuses rapidly, but its distriution is not uniform. Highest concentrations are found n liver and kidney, and lowest concentrations are found n brain and cerebrospinal fluid. Chloramphenicol eners cerebrospinal fluid even in the absence of menineal inflammation, appearing in concentrations about alf of those found in the blood. Measurable levels are lso detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport cross the placental barrier occurs with somewhat lower oncentration in cord blood of newborn infants than n maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**
   It is not recommended for the routine treatment of the typhoid carrier state.
2. **Serious infections caused by susceptible strains in accordance with the concepts expressed above.**
   a) *Salmonella* species
   b) *H influenzae*, specifically meningeal infections
   c) Rickettsia
   d) Lymphogranuloma-psittacosis group
   e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
c) The symptoms appeared in the following order:
   (1) abdominal distension with or without emesis;
   (2) progressive pallid cyanosis;
   (3) vasomotor collapse, frequently accompanied by irregular respiration;
   (4) death within a few hours of onset of these symptoms.
d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off

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*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

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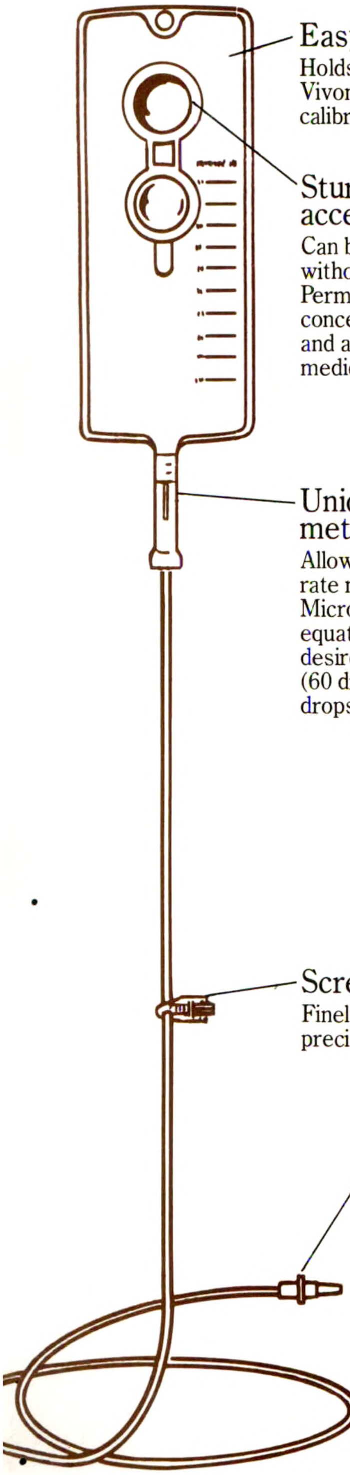

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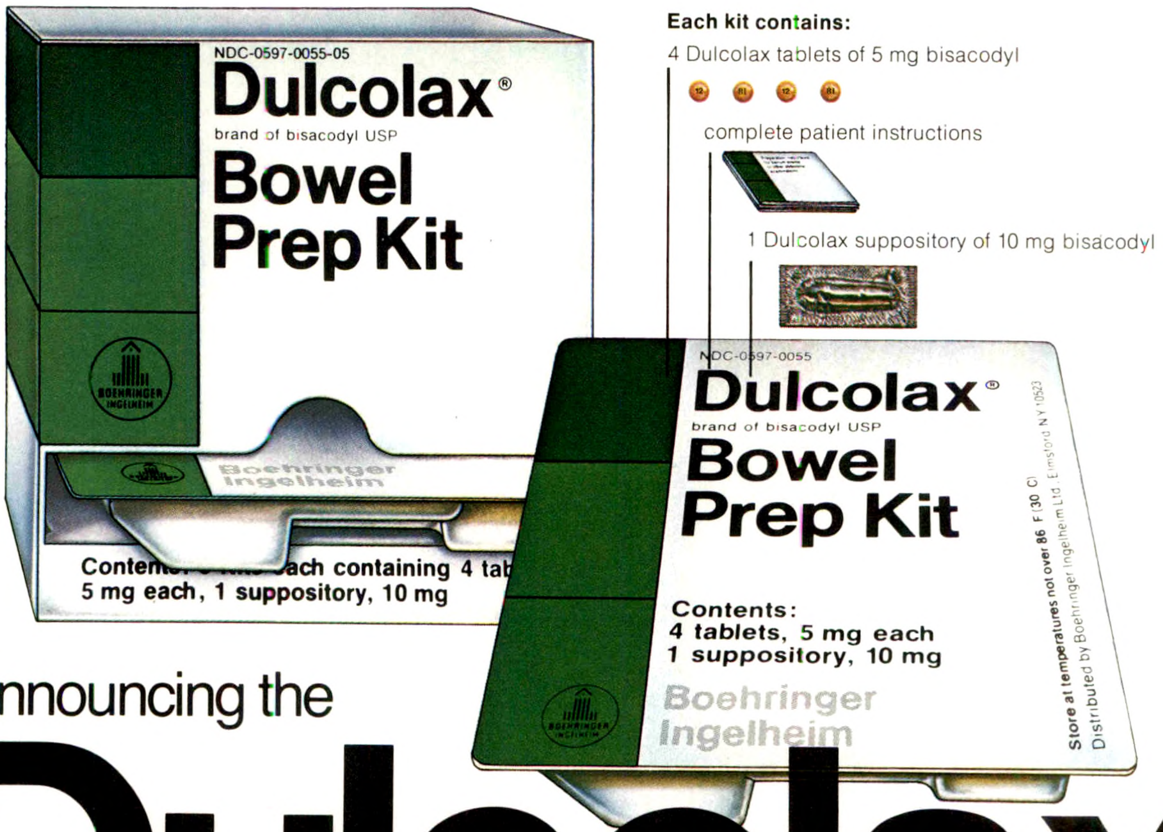

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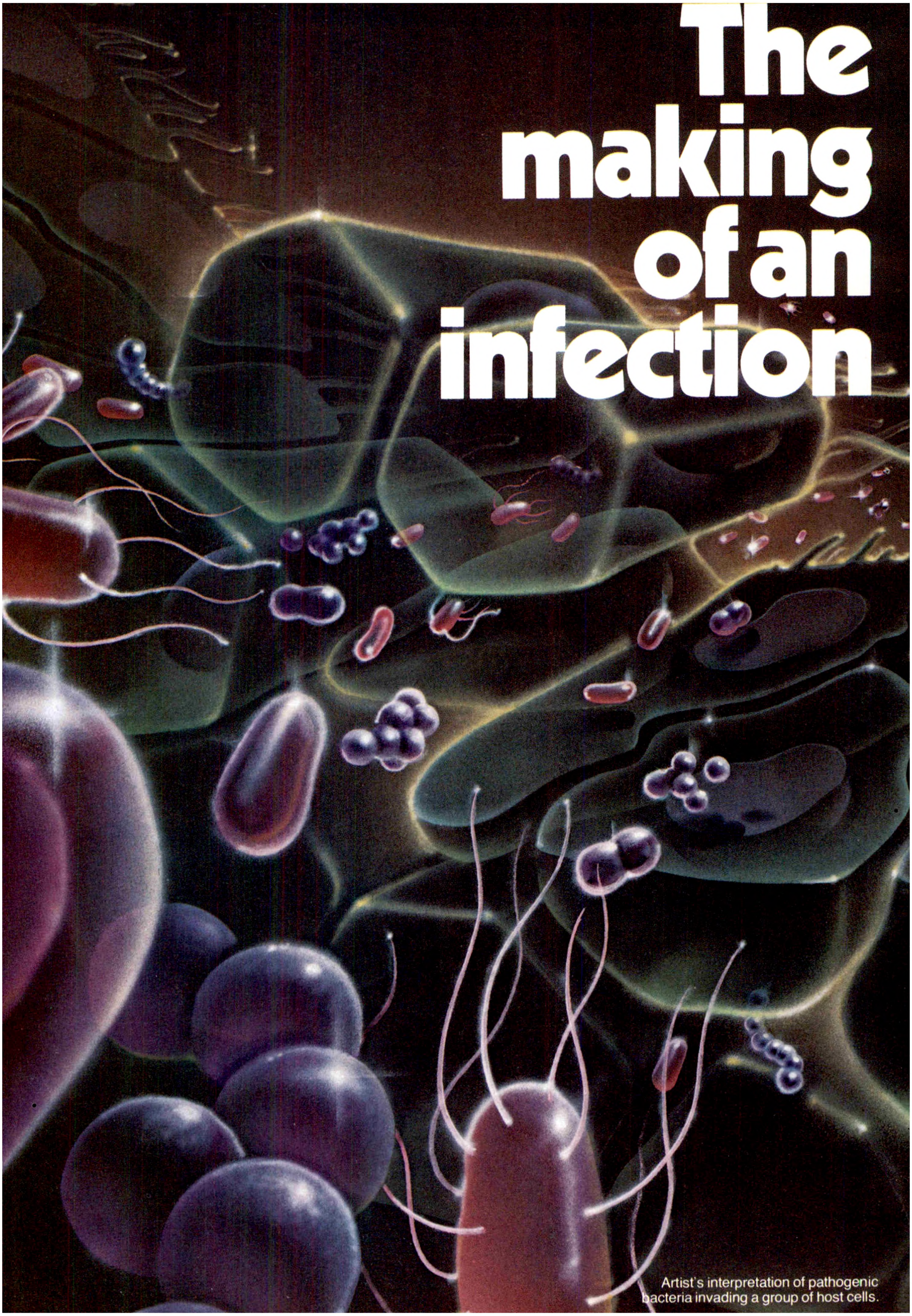
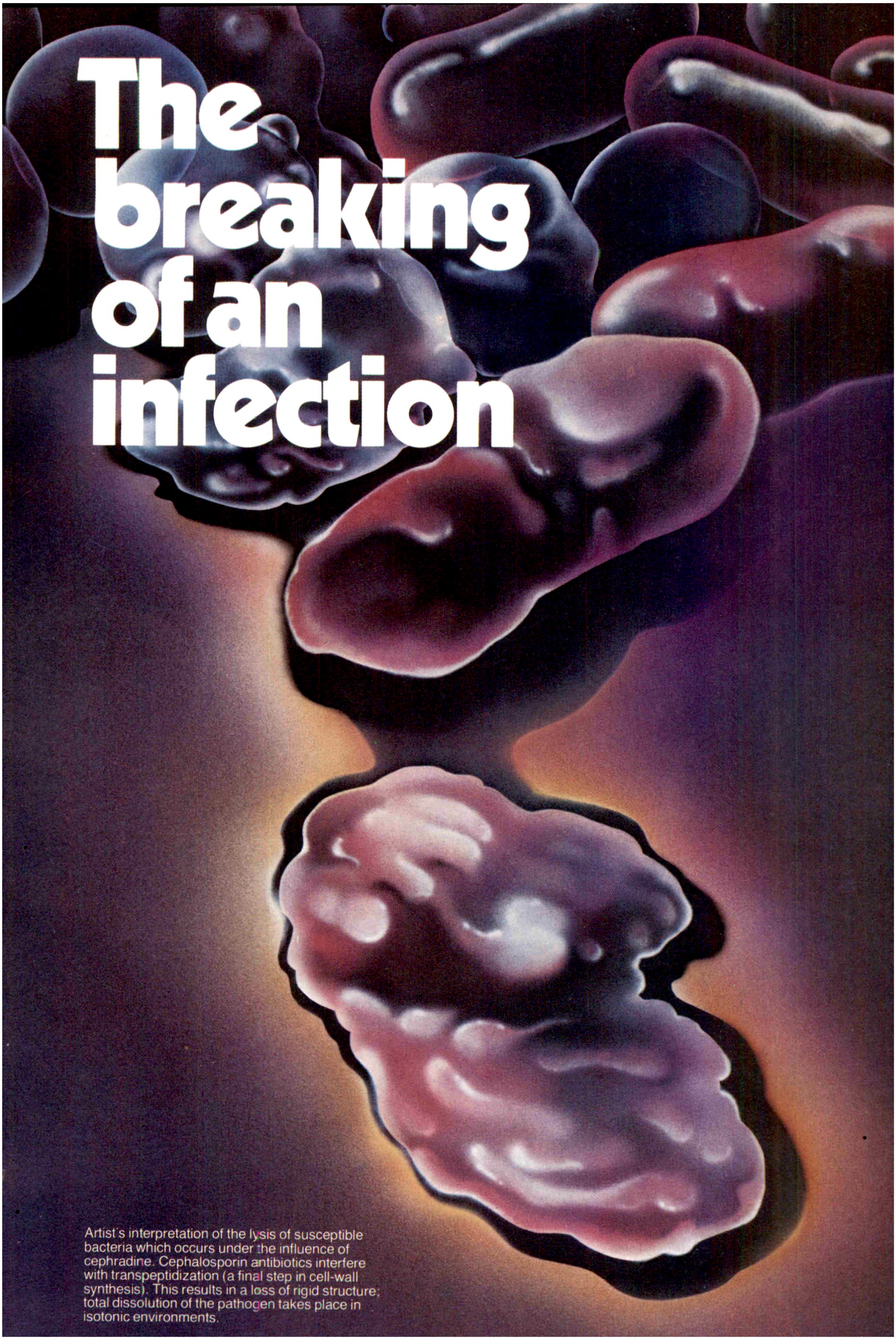


Artist's interpretation of pathogenic bacteria invading a group of host cells.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*Please see next page for Brief Summary, including susceptible organisms and b.i.d. and q.i.d. dosage schedules.

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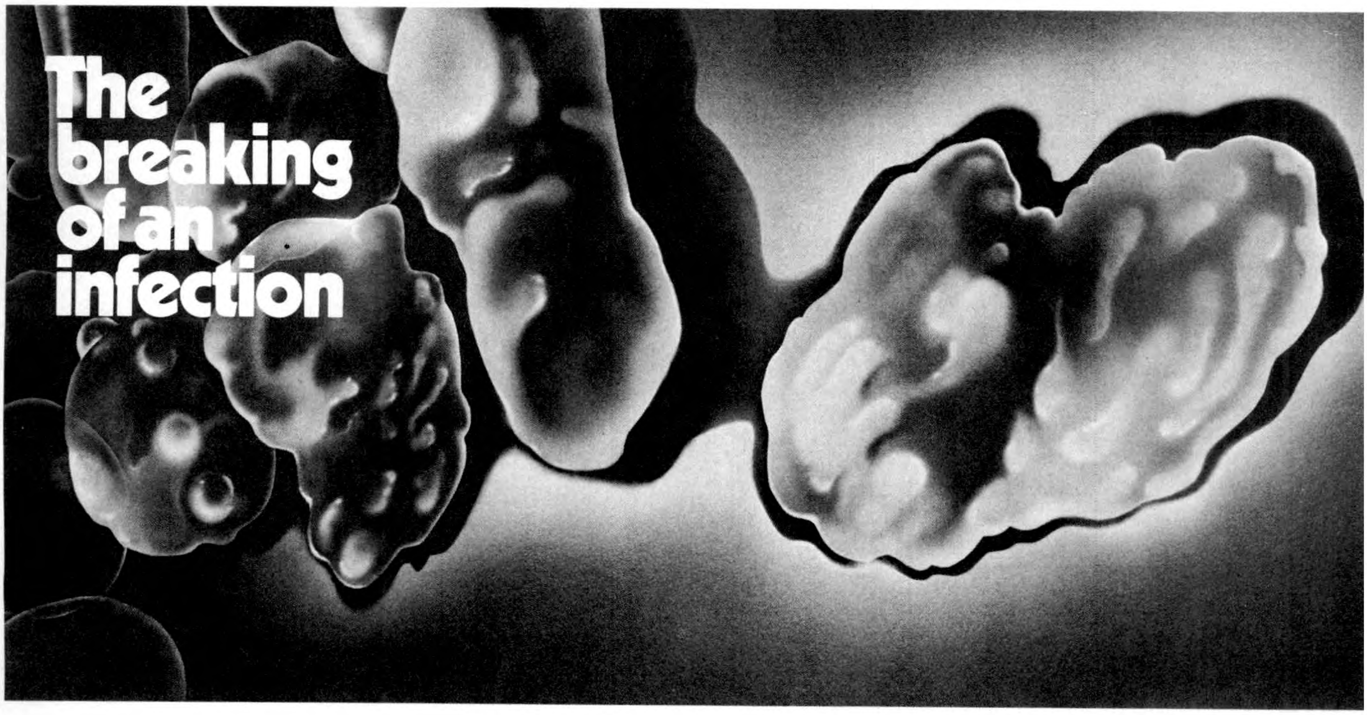
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Note: Culture and susceptibility tests should be initiated prior to and during cephradine therapy. Renal function studies should be performed when indicated.

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In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Usage in Pregnancy and Lactation: Although no teratogenic or anti-fertility effects were seen in reproduction studies in mice and rats receiving up to four times the maximum human dose, the safety for use in human pregnancy has not been established; weigh benefits in pregnant women against possible risk to the fetus. Cephradine is secreted in breast milk during lactation.

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Administer cephradine with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during cephradine therapy since cephradine accumulates in the serum and tissues. Patients with impaired renal function require a modified dosage schedule (see package insert).

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy.

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Recognize that a post-treatment positive Coombs test may be due to the drug since a false positive direct Coombs test has been reported after treatment with other cephalosporins.

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ANNALS OF SURGERY

Vol. 188 November 1978 No. 5

Management of Penetrating Carotid Arterial Injury

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A review of the experience with penetrating wounds to the carotid artery was undertaken in an effort to establish concise clinical criteria for surgical management. These results were compared with similar cases from the literature reported since 1963. In these 233 cases, the presence or absence of preoperative neurological deficits was correlated with vascular repair or ligation of the carotid artery.

The presence of coma preoperatively was the single most influential factor in determining operative management and prognosis. Patients without a neurological defect should have restoration of vascular continuity (0% mortality, 0.6% morbidity), which produces significantly better results than carotid ligation ($p < 0.002$). Patients with all grades of neurological deficit, short of coma, should also have primary vascular repair. Morbidity and mortality rates are significantly less than those following ligation (15 vs. 50%, $p < 0.05$). In comatose patients, neither repair nor ligation appear to influence the poor prognosis. At the present time, ligation of the carotid artery is only indicated in the comatose patient who has no evidence of prograde flow or if repair is technically impossible.

FOLLOWING THE CONFLICT in Southeast Asia a number of civilian and military reports were published in an effort to review results of treatment and to establish guidelines for the management of carotid arterial injuries.[2–4,8,13,16,17] These reviews focused on the preoperative neurological status of the patient and attempted to establish guidelines for repair based on the presence or absence of neurologic deficits. The conclusions were vague, however, leaving the surgeon without specific criteria on which to base treatment. This report reviews a ten year experience at the Medical College of Virginia of isolated common and internal carotid arterial injuries in 18 patients. Comparison of the outcomes with the published reports of results in a total of 215 cases has allowed us to develop specific clinical guidelines for management of carotid arterial injuries.

Patients and methods

From January 1966 to December 1975, 96 patients with penetrating injuries to the neck underwent surgical exploration at the Medical College of Virginia, Virginia Commonwealth University. Eighteen of them had isolated injuries to the common or internal carotid arteries. Those patients who had associated injuries that might have influenced their clinical course were eliminated from review, as were those with isolated external carotid or venous injuries.

The delay from time of injury to surgical intervention could be determined accurately in 12 cases and the mean interval was 195 minutes. Seventeen of the 18 patients were male and the age range was from 19 to 70 years with a mean of 31 years. There was an equal distribution of right and left sided injuries. Sixteen wounds were inflicted by low caliber gunshot wounds and there were two penetrating injuries from knife wounds.

A thorough neurological evaluation was performed preoperatively in each patient. The comatose state was defined as unresponsiveness to verbal stimuli. Systemic hypotension defined as systolic blood pressure less than 90 mmHg was present on admission in seven patients and was corrected preoperatively in each case. Student's t-test was used to determine significance of difference between groups.

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Submitted for publication: March 28, 1978.

Supported in part by U.S. Navy Contract #N00014-76-C-0422.

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TABLE 1. *Results of Surgical Repair of Carotid Artery Injuries in Patients without Preoperative Neurological Deficits at the Medical College of Virginia 1966–1976*

Sex	Age	Mode of Injury	Injury*	Assoc Injury	Operation	Preoperative Neuro Status	Postoperative Neuro Status	Shunt	Comment
M	19	GSW	C.C.	None	Resection & primary anastomosis	Normal	No deficit	Yes	Normotensive: ischemic time 4 minutes
M	70	GSW	C.C.	None	Lateral arteriorrhaphy	Normal	No deficit	Yes	Normotensive
F	58	GSW	C.C.	None	Resection & primary anastomosis	Normal	No deficit	No	Normotensive: ischemic time 12 minutes
M	24	GSW	C.C.	Left linear skull	Resection & primary anastomosis	Normal	L. hemiparesis	No	Hypotension corrected preoperatively; developed hemiparesis on 5th post-op day. Emergency right frontal lobectomy
M	20	GSW	C.C.	None	Saphenous vein graft CC to IC	Normal	Transient paresis, right arm	Yes	Normotensive: cleared completely
M	50	Stab	C.C.	None	Resection & primary anastomosis	Normal	No deficit	No	Hypotension corrected preoperatively
M	32	GSW	C.C.	None	Ext. jugular vein patch C.C.	Normal	No deficit	Yes	Normotensive
M	35	GSW	C.C.	A-V fistula	Resection & primary anastomosis	Normal	No deficit	Yes	Normotensive
M	24	GSW	I.C.	None	Lateral arteriorrhaphy	Normal	No deficit	No	Normotensive
M	20	Stab	C.C.	None	Dacron patch graft to C.C.	Normal	No deficit	No	Hypotension corrected preoperatively. Respiratory arrest necessitating tracheostomy in E.R.

* CC = Common carotid artery; IC = Internal carotid artery.

Results

There were no correlations among hypotension, neurological deficit and the end result (Tables 1 and 2). Four patients had significant neurological deficit and associated hypotension. However, correction of hypotension did not improve the neurological deficit. There were four deaths for an overall mortality rate of 22%. All deaths occurred in the immediate postoperative period (*i.e.*, within 72 hours) and were related to cerebral injury. Postmortem examination was obtained in one of the patients and showed macroscopic evidence of hemorrhagic infarction. The second patient who died had a clinical course compatible with uncal herniation. The third death followed 12 hours of generalized seizure activity. Subsequent EEG's showed no evidence of cerebral activity. In the fourth patient, disseminated intravascular coagulation complicated the clinical picture, although the neurological status of the patient was unchanged following surgery.

Absence of Preoperative Neurologic Deficit

On the basis of the preoperative neurological examination, ten patients showed no deficit (Table 1). All had primary vascular repair of their arterial injuries and nine of them are now alive and well without neurological sequelae. One patient (Case #5) had a transient monoparesis which cleared completely. Another patient (Case #4) developed a left hemiparesis postoperatively. This patient had a benign course until the fifth postoperative day when he developed a left hemiplegia and rapidly became comatose. He underwent emergency cranial decompression by right frontal

TABLE 2. *Results of Surgical Repair of Carotid Artery Injuries in Patients with Preoperative Neurological Deficits at the Medical College of Virginia 1966–1976*

Sex	Age	Mode of Injury	Injury*	Assoc Injury	Operation	Preoperative Neuro Status	Postoperative Neuro Status	Shunt	Comment
M	20	GSW	C.C.	Fracture mandible	Ligation common carotid bifurcation	Unresponsive sluggish pupils	No deficit	Yes	Normotension corrected preoperatively. Ischemic time 10 minutes
M	21	GSW	C.C.	None	Resection & primary anastomosis	R. monoplegia (arm)	Deficit cleared	Yes	Normotensive
M	19	GSW	C.C.	Transected spinal cord @ C-5 level	Resection & primary anastomosis	Unresponsive flaccid extremities	Death at 72 hrs.	Yes	Hypotension corrected in O.R. prior to surgery
M	26	GSW	C.C.	None	Saphenous vein graft C.C. to I.C.	Left hemiparesis	Deficit cleared	Yes	Normotensive
M	46	GSW	C.C.	None	Ligation common carotid	Comatose with right hemiparesis	Comatose Death	No	Normotensive; generalized seizure activity postoperatively. Death at 72 hours
M	21	GSW	C.C. I.C.	None	Resection & primary C.C. to I.C.	Comatose	Decerebration & death	Yes	Autopsy confirmed intracerebral hemorrhage
M	20	GSW	C.C.	Int. jug vein, soft tissue	Ligation right common carotid	Comatose	Comatose Death	No	Hypotension corrected preoperatively: DIC
M	30	GSW	C.C.	C.C.	Ligation common carotid	Comatose left hemiplegia	Unchanged	No	Hypotension corrected preoperatively. Death 2° aspiration 9 months postoperatively. Remained comatose

* CC = Common carotid artery; IC = Internal carotid artery.

lobectomy. The pathology report showed hemorrhagic infarction of the right frontal lobe. At two years follow-up, this patient is ambulatory with a brace and is under treatment for a seizure disorder.

Preoperative Neurological Deficit

In eight patients (Table 2), a significant neurological deficit was present preoperatively after hypotension had been corrected. The deficits consisted of monoplegia, hemiplegia or quadriplegia, with or without an associated comatose state. All of the deaths occurred in this group.

Four patients had operative repair of their vascular injury. Patients #12 and #14 had localized deficits manifested as monoplegia and hemiplegia, respectively and both of them cleared the deficit following revascularization surgery. Patients #13 and #16 were comatose and patient #13 was also quadriplegic. Both of them died within 72 hours following revascularization surgery.

An additional four patients were managed by ligation of the carotid artery. All of these patients were comatose at the time of surgery and three of them also had localizing neurological signs. There were two deaths in the group, one of which occurred nine months following surgery. One patient has shown improvement, and the fourth is fully recovered.

Collected Review

A number of reports related to carotid arterial injury have been published since 1963.[1–4,6,8,13,16,17] The preoperative and postoperative neurological status and operative management were determined in each published series. Those cases with associated head injury or any significant injury which could influence the outcome of the patient were eliminated. A total of 215 cases was obtained from this selective review. Combined with the cases from this study a total of 233 cases were available for analysis.

The cases were divided into four groups, cross

TABLE 3. *Collected Results of the Treatment of Carotid Artery Injuries in the Absence of Preoperative Neurological Deficit*

	Revascularized	Ligated
Treatment		
Previously published cases	151	9
Current report	10	0
Total cases	161	9
Results		
No deficit	153	6
Transient deficit	6	0
Permanent deficit	2	2
Death	0	1
Favorable outcome	99%*	67%*

* $p < 0.002$.

matching the presence or absence of preoperative neurological deficit with the method of management; *i.e.*, either restoration of vascular continuity or ligation of the damaged carotid vessel.

One hundred seventy patients had a normal neurological examination prior to surgery. One hundred sixty-one of them had direct repair of their injury. There were no deaths in this group but two patients developed hemiplegia as a residual neurological deficit (Table 3).[16]

Nine patients who had normal neurological examinations had the injured carotid vessel ligated. This was usually due to technical difficulty associated with attempts at repair. One death occurred in this group and two patients developed permanent neurological deficits.[4,13] Therefore a favorable outcome was significantly less likely ($p < 0.002$) after carotid artery ligation (Table 3).

Sixty-three patients had abnormal neurological examinations preoperatively. The deficits were monoplegia, hemiplegia, quadriplegia, aphasia, or coma. The comatose state was often found in conjunction with lateralizing signs. Forty-nine patients had restoration of vascular continuity. There were 12 deaths in this group and all of them were related to cerebral injury (Table 4). The remaining 14 patients were managed by ligation of the carotid artery. Forty-three per cent were no worse following surgery but 57% deteriorated or died following carotid artery ligation. There was no significant difference between this outcome and the 33% mortality rate associated with revascularization.

TABLE 4. *Collected Results of Treatment of Carotid Artery Injuries in the Presence of Preoperative Neurological Deficits*

Treatment		
Previously published cases	45	10
Current report	4	4
Total cases	49	14
Results		
Improved	23	5
Unchanged	10	1
Progressive deficit	4	1
Death	12	7
Favorable outcome	67%*	43%*

* Not significant.

TABLE 5. *Collected Results of Treatment of Carotid Artery Injuries in the Presence of Preoperative Neurological Deficit Exclusive of Coma (Total Cases Reported—40)*

	Revascularized	Ligated
Improved	22	2
Unchanged	7	1
Progressive deficit	2	1
Death	3	2
Favorable outcome	85%*	50%*

* $p < 0.05$.

If those patients who were comatose at the time of surgery are excluded, then the results following vascular repair as opposed to ligation are exceptionally good (Table 5). There were 34 patients who had significant preoperative neurological deficits (monoplegia, hemiplegia, aphasia) but without coma. Twenty-nine (85%) were improved or showed no deterioration from their preoperative state as opposed to a favorable outcome in only 50% of the ligated group ($p < 0.05$). Twenty-two patients who had vascular repair (65%) had a complete recovery with subsequent normal neurological examination. There was progression of the neurological deficit in two patients and three of them died.[4] It should be noted that in these three deaths no mention of the presence or absence of coma was made in the preoperative assessment. It is assumed that no coma was present; therefore, any bias would be directed against the conclusion that vascular repair is safe in the absence of coma. The fate of the comatose individual is bleak. Over 70% of comatose patients died regardless of the mode of therapy (Table 6).

Discussion

The current surgical literature including the most recent reports from Southeast Asia contains a number

TABLE 6. *Collected Results of Treatment of Carotid Artery Injuries in the Presence of Coma (Total Cases Reported—23)*

	Revascularized	Ligated
Improved	4	2
Unchanged	0	0
Progressive deficit	2	0
Death	9	6
Favorable outcome	27%*	25%*

* Not significant.

of pleas for more conservative approaches to management of patients with penetrating carotid injuries in association with severe neurological deficits.[2,4] Bradley, in an excellent review[2] which included a pathophysiological study of injury based largely on the primate experience of Denny-Brown and Meyer,[5,6–12] proposed that any injury with neurological lesions more severe than mild paresis, should be managed by ligation. Cohen[4] advocated the same approach following his military experience, except that he favored ligation in every patient with any degree of neurological impairment. Thal[16] recommended vascular repair only if flow was present in the carotid system at the time of exploration. The recent experience at the Medical College of Virginia and the review of published data do not support these conservative recommendations.

It is logical to assume that the presence of a preoperative neurological deficit is an indication of inadequate cerebral collateral blood flow. However, this assumes that those factors which influence collateral blood flow are corrected before determining the extent of the deficit. These factors include systemic hypotension, reduction in arterial oxygen tension and accumulation of acid metabolites.[9] On this basis, patients with penetrating carotid injuries can be divided into two groups: 1) those patients with adequate collateral flow as evidence by the absence of neurologic signs; 2) those patients with inadequate collateral circulation as demonstrated by the presence of a neurological deficit. The exception to this would be those patients with injury to the carotid system without total disruption of flow. In this group, the adequacy of collateral flow could not be assessed.

Ninety per cent of the cerebral blood flow is contributed by the carotid vessels and 10% by the vertebral system. If flow is interrupted in one of these vessels, there is a compensatory increase in flow in the other vessels supplying the circle of Willis.[7] However, only 20% of normal individuals have what is considered to be the standard anatomical configuration.[14] Other collateral pathways exist, but their importance in the acute disruption of flow is unknown.[2]

It seems apparent from the clinical results that the neurological state which correlates best with an irreversible injury is coma. Motor weakness or paralysis may be reversible with a very acceptable risk factor. Improvement therefore may be dependent on reestablishing blood flow to the ischemic area. Many believe that there is an area of relative ischemia surrounding an infarcted region which, although physiologically depressed, can improve with an increase in or restoration of cerebral blood flow. There is experimental evidence that permanent interruption by ligation of a major vessel decreases the reserve capacity of the brain to tolerate any vascular stress.[15] Consequently both the experimental evidence and the clinical data presented argue against carotid ligation.

The management of the comatose patient remains difficult. Results are similar regardless of which surgical approach is taken. It seems reasonable that if prograde flow is present in the injured carotid at the time of exploration, the revascularization should be attempted. If no flow is present and the patient is comatose, restoration of flow to this avascular area could be deleterious.

This study has focused on isolated carotid injuries in an effort to exclude any bias that associated injuries might have on the end result. Our experience with patients having carotid injury in association with multiple system derangements is small, but the extension of this treatment plan to the multiple injured patient appears logical. Obviously, the carotid injury must take high priority in the immediate management of these individuals.

Conclusions

All patients who do not have a neurological deficit should have restoration of vascular continuity. This method of treatment is associated with uniformly good results, does not subject the patient to permanent interruption of flow and its possible sequelae, and does not place the patient at greater risk due to the progression of atherosclerotic disease.

All patients who have a significant neurological deficit (monoplegia, hemiplegia, quadriplegia, or aphasia) short of coma, should also have primary vascular repair. This method of treatment has been shown to be significantly superior to carotid artery ligation.

In comatose patients, repair or reconstruction should be undertaken if prograde flow is present. Neither repair nor ligation appear to change significantly the basically poor prognosis.

At the present time, ligation of the carotid artery is indicated only: (a) for the comatose patient with no prograde flow; and (b) for technical reasons when repair is impossible.

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Extrahepatic Biliary Obstruction by Metastatic Colon Carcinoma

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Extrahepatic biliary obstruction can be caused by cancer metastatic from the colon to the lymph nodes adjacent to the bile duct. This report details our experience with eight such cases treated at the Massachusetts General Hospital in the last seven years. The interval between resection of the primary tumor and appearance of jaundice averaged 13 months. The location of the obstruction, preferably defined preoperatively by cholangiography, was low on the common duct in three cases and high in the porta hepatis in five. Relief of biliary obstruction was accomplished by biliary-enteric bypass (four cases), internal biliary stenting by permanent indwelling tube (two cases), or by portal irradiation (two cases). In addition to palliating the symptoms of obstructive jaundice, the period of comfortable survival appears to have been extended: the bypassed patients lived 13–38 months. Erosion of tumor into the duodenum, with resulting gastrointestinal hemorrhage, was an additional problem in three patients. Our overall experience illustrates the value of distinguishing this subgroup of patients from the larger number whose jaundice results from extensive liver metastases, and of treating aggressively those with extrahepatic biliary obstruction.

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JAUNDICE IS A COMMON late feature of uncontrolled colon carcinoma and usually signifies extensive hepatic metastases.[9,14] In this setting the onset of jaundice is a grave event, with a median subsequent survival time of only 33 days.[9] Death eventuates from hepatic failure due to replacement of the liver by cancer.

There is, however, a distinctly different subgroup of patients, whose jaundice is caused not by parenchymal destruction but by extrahepatic biliary obstruction. In these individuals metastases to lymph nodes behind the duodenum, along the common duct, or higher in the porta extrinsically compress the common duct. It has been our experience that the liver in these individuals is frequently free of gross metastases and that bypass operations to decompress the biliary tree may lead to comfortable survival for relatively long periods. We report here eight unselected cases to exemplify the potential for significant palliation of this complication of colon carcinoma.

Materials and Methods

From January 1, 1971 to December 31, 1977, we have treated or had direct contact with eight patients at the Massachusetts General Hospital who have proved to have extrahepatic biliary obstruction caused by colon carcinoma metastatic to nodes adjacent to the bile ducts. These patients are not the result of a search among all colon carcinoma patients seen at this institution (150 cases per year) and thus yield a minimum incidence of this phenomenon. Because we included all patients that we knew to have extrahepatic biliary obstruction due to metastatic colon carcinoma, the experience should be fairly representative. All patients were followed to death or to the present time.

Results

The cases are summarized in Table 1. Note that two of the patients were very young men. The spectrum of primary cancers was unremarkable. All were adenocarcinomas and all were invasive to mesenteric lymph nodes or through the serosa to surrounding structures at the time of the original colon resections. The interval between resection of the primary colon carcinoma and the appearance of jaundice averaged 13 months (range, 0–25 mo).

The jaundice was initially thought to be due to hepatitis in six of the eight cases. This erroneous clinical impression was based upon the general well-being of the patients in other respects. That is, they did not have the usual hallmarks of advanced cancer: weight loss, pain, fever, malaise, or fatigue. Blood chemistries, however, were typical of obstruction. Elevated alkaline

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Submitted for publication: March 27, 1978.

0003-4932/78/1100/0593 $00.75 © J. B. Lippincott Company

TABLE 1.

Pt.	Age, Sex	Primary Cancer	Interval to Onset of Jaundice (months)	Maximum Bilirubin (mg/100 ml)	Level of Bile Duct Obstruction	Method of Biliary Decompression	Survival after Decompression (months)	Other Treatment
1	66, F	Sigmoid	0	16	Duodenum	Choledocho-jejunostomy	38	Stenting through re-obstruction at 2 years
2	67, F	Sigmoid	5	14	Hilum	Right hepatic cholangio-jejunostomy	17	5-FU (no benefit)
3	22, M	Ascending colon	10	10	Duodenum	Choledocho-jejunostomy, gastrojejunostomy	36	Splenorenal shunt 2 years later
4	21, M	Transverse	24	6	Hilum	T-tube	1	None
5	68, F	Hepatic flexure	10	9	Duodenum	Choledocho-jejunostomy, gastrojejunostomy	13	3000 r, 5-FU+ BCNU (no benefit)
6	63, M	Rectosigmoid	25	20	Hilum	3750 r	14	Ligation and embolization of bleeding malignant duodenal ulcer at 6 months
7	56, M	Cecum	12	10	Hilum	4000 r	5	5-FU (no benefit)
8	58, F	Sigmoid	21	28	Hilum	Transhepatic tube	10 (living)	5-FU

phosphatase and elevated conjugated bilirubin were the predominant abnormalities, with lesser increases in transaminases. The nature and exact location of the obstruction were demonstrated by percutaneous transhepatic cholangiography (Fig. 1), endoscopic retrograde cholangiography (Fig. 2), or operative cholangiography (Fig. 3). In three cases the obstruction was located at the lower common duct at the level of the duodenum, and in five it was high in the porta at the hepatic duct bifurcation. In seven of eight patients there were no apparent liver metastases at the time of onset of obstructive jaundice. The eighth patient had one 2 cm nodule in the left lobe of the liver.

The three lower common duct obstructions were treated by Roux-en-Y choledochojejunostomy. Two of these were complemented by gastrojejunostomy because of invasion of the duodenum as well. The five high obstructions were treated by hepaticojejunostomy (Case 2), by insertion of a T-tube past the obstructed point (Case 4), by placement of a percutaneous transhepatic tube past the tumor down into the common duct (Case 8), or by radiation therapy (Cases 6 and 7).

Palliation was good to excellent in all successfully bypassed cases. Survival in these patients ranged from 13 to 38 months. Two patients were asymptomatic for more than two years (Fig. 4) and one for more than one year. One of the long-term survivors (Case 1) was reoperated upon 26 months after choledochojejunostomy and a tube inserted through the anastomosis to reestablish bile drainage past the enlarging tumor which had reobstructed bile flow. The other long-term survivor (Case 3) had a splenorenal shunt 25 months after bypass because of splenic and portal vein obstruction causing portal hypertension and bleeding esophageal varices.

Bleeding from malignant ulceration into the duodenum (Fig. 5) was a major recurrent problem in three patients (Cases 1, 3 and 6), requiring transfusion therapy and further operations.

Postoperative adjunctive chemotherapy was used irregularly and without apparent benefit. Irradiation of the portal nodes was used in three cases, once (Case 6) producing complete and sustained relief of jaundice.

Discussion

Metastases to lymph nodes along the common duct and in the port hepatis may originate from primary carcinomas of the colon,[7] breast,[12] lung,[1] as well as from melanoma[6] or lymphoid neoplasms.[3,7] It is of particular importance that, at least with colon carcinoma, these periportal nodal metastases seem to occur surprisingly frequently without tumor in the liver itself, for "It is the presence of hepatic metastases rather than any associated extrahepatic spread of the neoplasm which governs prognosis."[9] When the liver contains metastases from colon cancer, the median survival time ranges from three to ten months,[4,9,13,14] but median survival is only 33 days after the appearance of jaundice due to hepatic metastases.[9] In contrast, median survival is 23 months when only lymph nodes are involved by metastases.[13] Survival with advanced intra-abdominal colon cancer, futhermore, significantly exceeds the survival with comparable stages of other gastrointestinal malignancies: median survival time after palliative surgery for colon cancer in 9.7 months but only four months for other intra-abdominal cancers.[4] Thus, in several ways the type of patient under consideration in this report has a more favorable prospect for prolonged palliation. Among the seven who have died at this time, mean survival time *after appearance of jaundice* was 18 months and the median survival was 14 months.

The biliary-enteric bypass in any given case will vary with the circumstances. The duodenum, as a general rule, should not be used because it is or will be invaded by tumor. A Roux-en-Y limb of jejunum will insure a greater time interval before reobstruction. For similar reasons the anastomosis to the biliary tree should be as high as possible on the bile duct. The gallbladder should not be used because the level of biliary obstruction is usually at or higher than the cystic duct orifice, manifested by a collapsed gallbladder. The level of obstruction may in fact be high enough to necessitate intrahepatic anastomosis, the left hepatic duct being the easier to find and use.[2] In some cases of obstruction at the bifurcation it may be preferable to try the new technique of transhepatic passage of a tube down the bile duct, through the area of obstruction to the duodenum. This tube has side holes cut into it above and below the tumor and is left indwelling. Such tubes may be placed during laparotomy[5] or by percutaneous hepatotomy.[11] The tube can be replaced if it becomes occluded by debris.

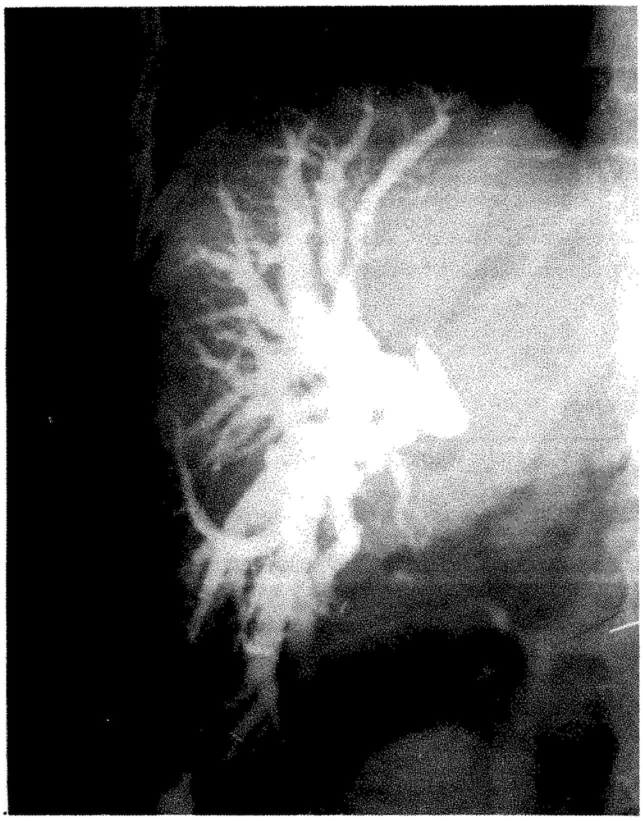

FIG. 1. Percutaneous transhepatic cholangiogram (Case 2) showing complete obstruction of the bile ducts in the porta. There is no apparent communication between the right and left hepatic duct systems.

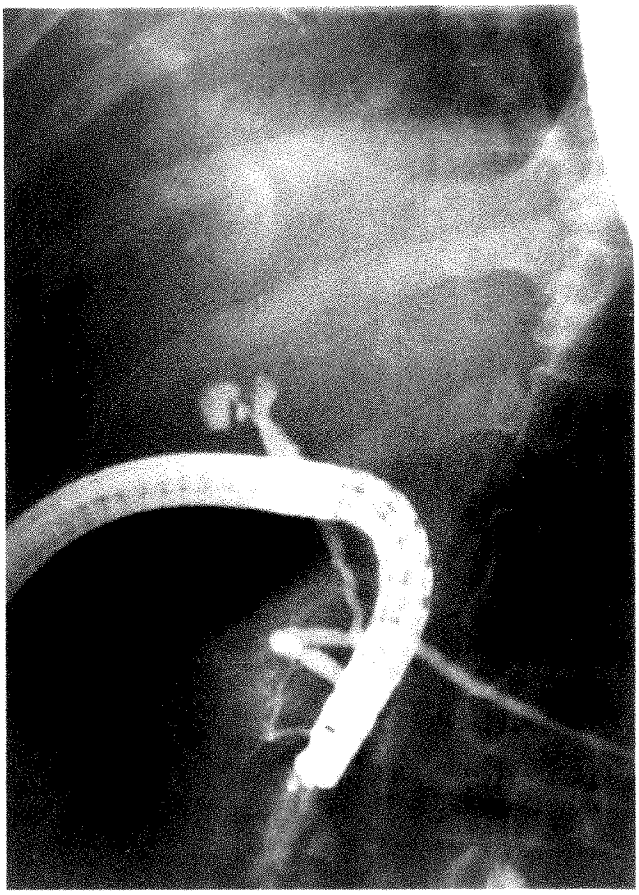

FIG. 2. Endoscopic retrograde cholangiogram (Case 8) showing complete obstruction of the common hepatic duct. Note the origin of the cystic duct below the obstruction.

Invasion of the duodenum from metastases in retroduodenal nodes occurred in three of eight patients in this series and was responsible for ulceration and bleeding. Consequently we consider it advisable to perform a gastrojejunostomy to complement the biliary bypass in most cases. Defunctioning the duodenum by stapling or

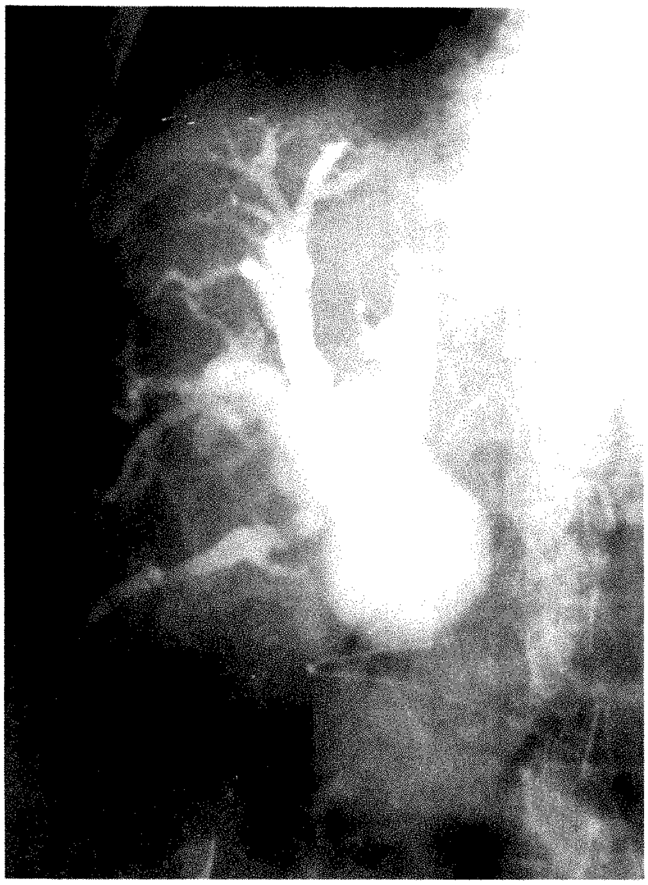

FIG. 3. Operative cholangiogram (Case 1) showing a massively dilated common duct with obstruction at its lower end.

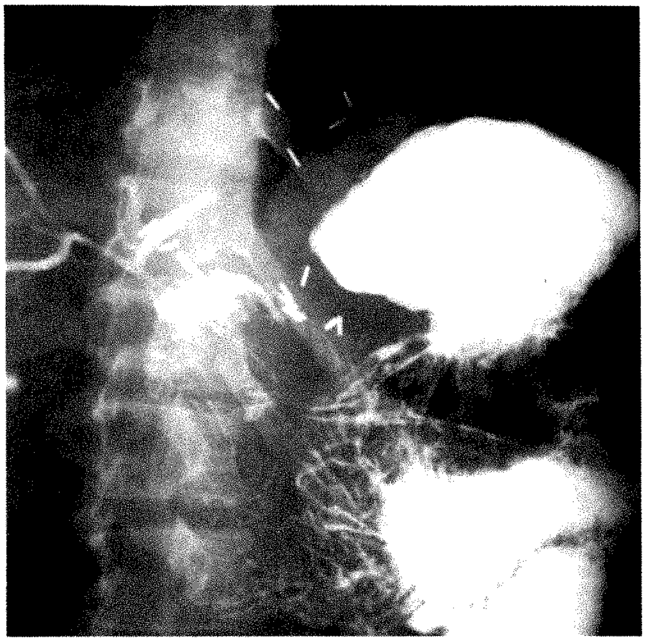

FIG. 4. Upper GI series two years after choledochojejunostomy (Case 3). The biliary tree remains completely decompressed.

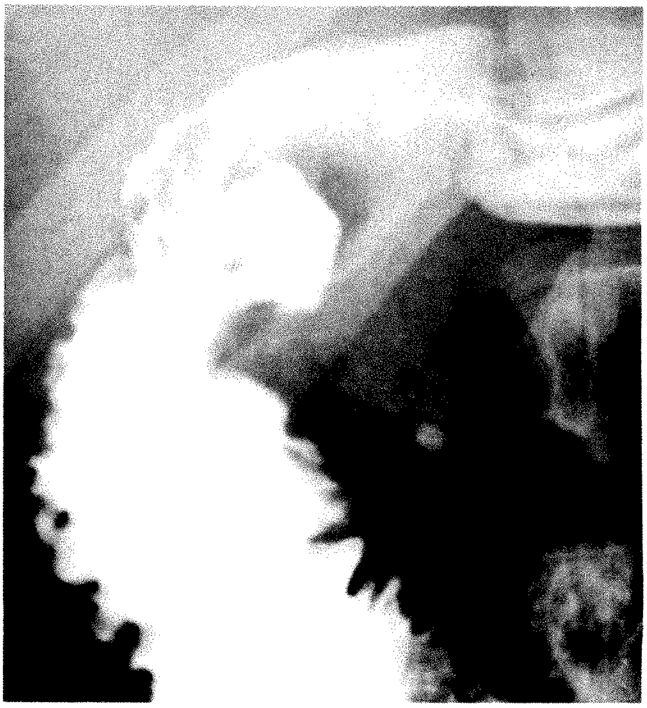

FIG. 5. Barium study of the duodenum (Case 3) showing a large postbulbar ulcer. This was proven at surgical exploration to be ulceration in a tumor mass eroding through the posterior wall of the duodenum.

suturing the pylorus closed has in our experience seemed to reduce the amount of blood loss from the malignant duodenal ulcer (personal observation).

Biliary bypass in patients with extrahepatic biliary obstruction from metastatic colonic cancer offers not just palliation of pruritus and other symptoms of biliary obstruction, but appears to prolong life. It is unlikely that our one to three year survivals would otherwise have been possible in the face of high-grade jaundice. The prolongation of life by biliary bypass in this circumstance distinguishes it favorably from the biliary obstruction caused by pancreatic and periampullary cancer. Median survival time with these latter forms of malignant biliary obstruction is three to five months[4,5] and is *not* lengthened by palliative bypass.[4,15] Whether adjunctive chemotherapy or radiation therapy can provide any additional advantages cannot be answered from our experience, but there has been particular reawakening of interest in local irradiation of the portal area.[8,10]

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Fungal Infections in Renal Transplant Recipients

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Infection continues to be a major source of morbidity and the major source of mortality in renal transplant recipients who are susceptible to opportunistic infections. We recently reviewed all renal transplant recipients who had fungi cultured during a three year period. *C. albicans* and *T. glabrata* were cultured most frequently. Deep fungal infections occurred in many patients and were frequently observed late in the course of bacterial and viral infections. Ten patients had fungemia, and primary fungal pneumonia occurred in eight patients. Three patients had fungal infection of the central nervous system. Three of eight patients with fungal pneumonia and eight of ten patients with fungemia died as a result of their fungus infections. These patients frequently had poor renal function and were receiving high steroid doses or had recently been treated for kidney rejection. One patient with fungal pneumonia and six patients with fungemia had the fungus cultured from a superficial site. Several patients developed fungal infections late in the course of viral or bacterial infections. Amphotericin-B and 5-fluorocytosine remain the mainstays of antifungal therapy.

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INFECTION CONTINUES TO BE A MAJOR source of morbidity and mortality in renal transplant recipients and in other immunosuppressed patients.[5,10,12–15,17,18,22,27] The most common causes of serious illness and death in transplant patients are bacterial infections—especially Staphylococci and the Gram-negative enteric bacteria.[1,8,23] Viral infections,[9,22,25] and protozoal infection—*Pneumocystis carinii*—also can cause lethal infections in immunosuppressed patients.[23]

Fungal infections, too, cause disease and death in transplant recipients.[3,5–7,11,15–17,19,23] There is a relatively high incidence of primary fungal pneumonia and meningitis, and several reports suggest that urinary tract or mucosal surface infections can serve as sources for deep infections.[17] In addition, the high incidence of fungal infections has been blamed on the "indiscriminate use of antibiotics" in these patients. No one has correlated the incidence and severity of deep fungal infections with the incidence of fungal contamination of superficial sites. Some of the reports are derived from transplant centers where antimicrobial agents are given to all patients.

To ascertain a truer incidence of fungal contamination of the urine and of superficial sites (mouth, throat, nasopharynx), we examined all fungal cultures from our renal transplant recipients for a three year period. We also reviewed patients with deep fungal infections to determine whether predisposing causes and modes of clinical evidence were present. Almost all transplant recipients at this center have received antimicrobial prophylaxis.

Patients and Methods

The subjects of this report are all transplant recipients who had fungus detected by culture during a three year period from January 1, 1974 to December 31, 1976 (544 patients were transplanted prior to 1974 and 356 patients were transplanted after 1974). Approximately 60% of the recipients were male, 60% received kidneys from cadaver donors, and 35% had renal failure caused by juvenile onset, insulin dependent, diabetes mellitus. A combined bilateral nephrectomy and splenectomy procedure usually preceded each transplant. Standard posttransplant immunosuppressive therapy was used—antilymphoblast globulin (30 mg/kg for 14 days), maintenance azathioprine (1.5–2.5 mg/kg/day), and maintenance prednisone (0.25–0.33 mg/kg/day).[24] Rejection episodes were treated by increasing the prednisone dosage to 2 mg/kg/day and tapering it gradually to 0.5 mg/kg/day one month later. Azathioprine dosage is never increased.

For antimicrobial prophylaxis our transplant patients receive dicloxacillin for 21 days. They also swish and swallow 100,000 units of nystatin four times a day for one month, and nearly all patients receive sulfasoxazole (1 g four times a day) indefinitely.

Before transplantation routine culture mediums of the throat, sputum, and urine (or bladder irrigation) are prepared for bacteria, fungi, and viruses. These

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Submitted for publication: December 12, 1977.

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TABLE 1. *Fungi Cultured from Superficial Sites in 181 Transplant Recipients*

Fungi	Urine	Throat	Sputum	Stool	Mouth	Vagina	Naso-pharynx	Shunt & IV
Candida								
albicans	64	80	36	30	6	4	1	2
other species	2	2	2	1				
Torulopis								
glabrata	21	5	2	6		2		
Crytococcus								
neoformans	1							
Aspergillus								
niger		1						

tests are repeated whenever a patient returns to the hospital. If the patient is febrile, cultures of the blood, nose, throat, sputum, and urine are repeatedly taken. Transtracheal aspiration has been an inefficient means of diagnosing pulmonary infections, and has caused local neck infections in these immunosuppressed patients. Instead, we perform bronchoscopy,[2] promptly. We seldom use a lung biopsy for the diagnosis of pulmonary infiltrates.

Specimens for fungal isolation are plated on inhibitory mold media, brain–heart infusion agar, and mycobiotic agar (Gibco Diagnostics, Madison, Wisc.) and incubated in air at 30° for 30 days. Some fungi (*Histoplasma capsulatum*) can take up to 25 days to grow.

Results

Superficial Sites

Four species of fungi were cultured from eight superficial sites in 181 transplant recipients (Table 1). Of these 181 patients, only 18 (10%) developed a deep fungal infection or fungemia with an organism that had been previously cultured from a superficial site. In these patients the fungal contamination of the urine, or epithelial, or mucosal surface may have served as a focus for fungal infection of a deeper site. Six of the eight patients with fungemia caused by *Candida albicans* had the yeast previously cultured from superficial sites (five from the urine and one from the throat). One patient who had pneumonia due to *Candida albicans* also had the fungus in the urine and throat. The one patient with *Cryptococcus neoformans* cultured from the urine, also had it in his cerebrospinal fluid. The patient with *Torulopsis glabrata* cultured from the peritoneal fluid, previously had it in the urine—a bladder leak, that communicated with the peritoneal cavity, developed after transplantation. Ten of the 12 patients with contamination of wound infections also had the fungi cultured from the urine (nine patients) or sputum (one patient). Only two wound infections were contaminated with, or infected by, fungi which had not been previously cultured from a superficial site.

Only six patients with involvement of a superficial site were treated with antifungal agents. Two of these had infection of the mouth (thrush) with *Candida albicans* and were treated successfully with nystatin mouth washes. The four others received nystatin suppositories for vaginitis caused by *Candida albicans*.

Deep Sites

Wounds. Twelve patients had fungi cultured from wounds (Table 2). Eleven of the 12 wound infections were contaminated with *C. albicans. Torulopsis glabrata* as cultured from one wound. None of these infections was a primary infection because bacteria were also cultured. In several instances the fungus was only cultured after the wound had been opened, drained, and treated with antibiotics.

None of these patients was treated with antifungal agents, because the fungus was considered to be a wound contaminant. In no instance was it associated with local or distant tissue invasion. There were eight

TABLE 2. *Fungi Cultured from Deep Sites in Transplant Recipients*

Fungi	Wound	Perito-nium	Central Nervous System	Kidney Graft	Lung	Blood
Candida						
albicans	11	2		2	5	8
Torulopsi						
glabrata	1	1				
Aspergillus						
fumigatus					1	
niger						
flaves					1	
Cryptococcus						
neoformans			2			1
Histoplasma						
capsulatum				1	2	2
Coccidiodes						
immitis			1			

combined fungal and bacterial infections around transplanted kidneys and all were treated by nephrectomy. Although all of these patients died, three of them had recovered from their deep wound infection.

Peritonium. Three patients had yeasts cultured from the peritoneal cavity. All three also had concomitant bacterial peritonitis within two months of transplantation. All three were receiving more than 0.5 mg/kg/day of prednisone, and two had serum creatinine levels greater than 2.1 mg/dl.

One patient with diabetes mellitus underwent total gastrectomy because of hemorrhagic gastritis. She developed Candida and bacterial peritonitis caused by a leak from the esophogojejunostomy. Candida had been cultured from the throat and probably found its way into the peritoneal cavity from swallowed saliva. She died of bacterial peritonitis. Although Candida had been cultured from the peritoneal cavity during exploration for the leak from the esophogojejunostomy, none was found at postmortem examination, ten days after treatment with amphotericin B was begun. The second patient, a 40-year-old diabetic woman, developed a bladder leak into the peritoneal cavity two months after receiving a transplant from a cadaver donor. The bladder was reclosed. The peritoneal fluid contained *Torulopsis glabrata* (*T. glabrata* had been repeatedly cultured from the urine) and *Serratia marcescens*. She was treated with amphotericin-B and tobramycin. She still has normal renal function 48 months later. The third patient, a 20-year-old diabetic man, had primary peritonitis caused by Salmonella five days posttransplant. He was treated with gentamycin and had a laparotomy seven days later. Salmonella and *Candida albicans* were cultured from the peritoneum. He died 15 days after laparotomy. An autopsy revealed disseminated candidiases, without Salmonella.

Central nervous system. Three patients had fungal infections of the central nervous system. Two adult patients had meningitis caused by *Cryptococcus neoformans* 6–17 months posttransplant. Cryptococcus was not cultured from any other site. One patient had renal failure secondary to diabetes mellitus and the other had polycystic renal disease. Both had fever (38 and 38.5°) and mild headache. The white blood cell counts were 5,800 and 7,000 per mm^3. They were on maintenance doses of immunosuppression. In both cases the diagnosis was made after the immediate examination of the spinal fluid with an India ink preparation. Both patients recovered with systemic amphotericin-B and 5-fluorocytosine treatment, without intrathecal therapy.

Another patient had renal failure caused by Fabry's disease, and received a cadaver renal allograft. Five weeks after transplantation he became febrile (40°). Over the course of two weeks he became obtunded; he died five months after transplantation. Diagnostic tests, including repeated spinal taps and brain biopsies gave no cause for his decline. He never responded to either antibacterial or antifungal treatment. Autopsy findings included *Coccidioides immitis* that involved the brain, lungs, and kidney.

Kidney graft. Two patients had *Candida albicans* cultured from their transplanted kidneys. One, a diabetic, had *C. albicans* cultured from a lymphocele three months before laparotomy for a suspected abscess was performed. Instead, bacterial peritonitis was found so a transplant nephrectomy was performed. *Candida albicans* was cultured from the kidney specimen. The patient died four days later of bacterial peritonitis. In the other patient, *Candida albicans* was cultured from the kidney after transplant nephrectomy for chronic rejection. She recovered without further treatment and is now on maintenance hemodialysis.

Lung. Eight patients (age range 17–52 years) had primary fungal pneumonia (Table 3). One-half of the infections were recognized four to seven months after transplantation. Pneumonia occurred from 27 to 72 months posttransplant in the other four. One patient had a normal temperature, and the other seven had fevers between 38.5 and 39.5°. The eight patients had white blood cell counts of between 3,550 and 19,000 per mm^3; only two had white blood cell counts above 10,000 per mm^3.

Five of the patients had poor graft function with serum creatinine levels greater than 2.1 mg/dl. Although seven of them had been treated for at least one rejection episode, only one patient was receiving more than 25 mg/kg/day at the time he developed fungal pneumonia. Four of the patients had recently been treated for rejection episodes.

Four patients had fungal pneumonia caused by *Candida albicans*, two had pneumonia caused by *Histoplasma capsulatum*, and two had Aspergillus cultured from the lung (one of these also had Cryptococcus). Two patients also had bacteria isolated from the lung and were treated with antibiotics, in addition to antifungal agents.

Three patients died as a direct consequence of persistent fungal pneumonia. One patient (No. 4, Table 3) with pulmonary histoplasmosis (he also had *Histoplasma capsulatum* cultured from the blood) was found to have it in the liver as well. Two additional patients have died subsequently, one (No. 3, Table 3) died one year after successful treatment for pneumonia caused by *Histoplasma capsulatum*, but the autopsy results revealed disseminated *Herpesvirus hominis*. The other patient (No. 1, Table 3) died of liver failure after a second kidney transplant. Three patients are cur-

TABLE 3. *Fungal Pneumonia in Renal Transplant Recipients*

Patient # Sex Age	Primary Disease	Graft Donor	At Time of Infection		Months to Infection	Fungus	Other Infection Sites	Other Organisms Sites	Treatment	Outcome/Organism
			Serum Creatinine (mg/dl)	Prednisone (mg/day)						
1 F 21	CGN*	Rel.	4.8	10	60	C. albicans	—	E. coli, alpha, streptococcus lung	Amphotericine-B	Recovered—died of hepatitis and cirrhosis following second transplant
2 M 52	Polycystic kidney disease	Cad.	3.0	15	6	C. neoformans A. fumigatus	—	CMV† urine	Amphotericin-B	Recovered
3 F 35	Diabetes	Cad.	0.9	15	36	H. capsulatum	—	—	Amphotericin-B 5-fluorocytosine	Recovered—died one year later of disseminated *Herpesvirus hominis*
4 M 48	CGN	Cad.	1.6	20	72	H. capsulatum	—	—	Amphotericine-B 5-fluorocytosine	Died—disseminated H. capsulatum, gastric erosion
5 F 47	Polycystic kidney disease	Cad.	6.6 dialysis	20	27	C. albicans	Urine Throat	CMV urine	Amphotericine-B 5-fluorocytosine	Died three months after pneumonia C. albicans not found at autopsy
6 M 33	Diabetes	Rel.	1.5	22.5	7	C. albicans	—	—	Amphotericine-B	Recovered
7 F 17	Diabetes	Cad.	1.1	22.5	6	C. albicans	—	—	Amphotericine-B 5-fluorocytosine	Recovered
8 F 26	Diabetes	Cad.	4.4	10	4	A. Flavus	—	CMV sputum staphylococcus-throat	Amphotericine-B	Died—Aspergillosis of lungs, esophagus

* CGN = Chronic glomerulonephritis. † CMV = cytomegalovirus.

rently alive 18, 36, 38 months posttransplant. Two have normal renal function and the other is on maintenance hemodialysis.

Occasionally *Aspergillus fumigatus* is cultured from the lungs on postmortem examination although it is not recognized prior to death. It is our impression that patients who die after a prolonged illness from some other cause are the ones in whom Aspergillus is found at autopsy. Consequently, only patients who had fungus recognized in the lungs prior to death are included in Table 3. Four other patients had Aspergillus identified in the lungs on postmortem examination; all had died of bacterial sepsis. Aspergillus infection apparently occurs just prior to death. Because this type of fungal involvement does not appear to play any role in a patient's course, and because it is seldom recognized premortem, we have not included these cases in this report.

Blood. Ten patients (age range 19–52 years) had fungus isolated from the blood (Tables 2 and 4).

Candida albicans was cultured from eight patients, *Cryptococcus neoformans* was obtained from one patient, and the blood of two patients contained *Histoplasma capsulatum* (two fungi were present in one patient). Fungemia occurred within two months of transplantation in eight patients; it occurred at five and 72 months in the other two.

Poor renal function was usually associated with fungemia. Only three of the ten patients had a serum creatinine level less than 1.7 mg/dl prior to the onset of infection. Three other patients required hemodialysis because of failure of cadaver donor transplants to function immediately. Nine of the ten patients were receiving large doses of prednisone (more than 30 mg/day). All patients had fevers (38.5–41.5°) during infection. The white blood cell (WBC) count ranged from less than 1,000–12,800 per mm^3. Six patients had a WBC count of 3,200 per mm^3 or less. This leukopenia preceded the fungemia by zero to 30 days. None of the patients previously had leukopenia. Fungemia was never associated with the indwelling central venous infusion catheters that they all had earlier in their treatment.

Seven of the ten patients had fungemia during a course of bacterial sepsis or cytomegalovirus infection, or both. In all seven cases the bacterial or viral infection preceded the fungal infection by five–45 days. One patient had infection with cytomegalovirus alone, two patients had bacterial sepsis but had no evidence of viral infection, and four patients had evidence of both bacterial and viral infection. Six of the eight patients who died had their fungemia for no longer than ten days, one had fungemia for 24 days, and one had fungus cultured from the blood 36 days before he died.

Six patients had the same fungus (*Candida albicans*) cultured from the urine or the throat that they had cultured from the blood. One patient had concurrent *Histoplasma capsulatum* fungemia and pneumonia, and another had Candida peritonitis as well as Candida septicemia.

Four of the patients developed gastrointestinal hemorrhage caused by gastric erosions. Three of these four patients had bacterial sepsis in addition to fungemia, and one had disseminated histoplasmosis but did not have concomitant bacterial or viral infection.

Amphotericin-B was used to treat seven of the ten patients. Four of them also received 5-fluorocytosine. Three patients received no antifungal agents because fungemia was not present until death from sepsis was imminent.

Of the two patients who survived the fungal septicemia, one patient had fungemia with *Cryptococcus neoformans* and died of heart failure one year after his second transplant. Only one of the ten patients is alive.

Postmortem examination was performed on seven of the eight patients. Residual fungus—usually in the lungs—was recognized in six of them, and the fungus was widely disseminated in three of them.

Treatment

Despite the emergence of several experimental antifungal agents, amphotericin-B is still the most effective drug for use against deep systemic fungal infections. Prolonged treatment with low doses, as recommended by Drutz, et al.[4] is the usual choice. We begin therapy with a total dose of 1 mg the first day, given over six hours and increase therapy to 0.5–1.0 mg/kg/day in five or six days. The higher doses are needed only for immediately life-threatening infection. The moderate doses can be given daily, or every other day to control nephrotoxicity. We have not had a permanent loss of transplant function that was attributable to amphotericin-B therapy.

Although the total dose of amphotericin-B recommended for patients with fungal infection is 2.5–3 g, there is no hard data to support that limit. The duration of therapy may be as meaningful a concept as dosage. Either way, the dose depends on the nature of the host, the fungus being treated, and the organ systems involved.[4] A method of determining dosage based upon the amount of amphotericin-B required to produce serum levels that inhibit the fungus is available. Using this method Drutz, et al.[4] found a total dosage range from 460 to slightly over 2,000 mg for disseminated histoplasmosis. Our current policy is to maintain amphotericin-B therapy for a minimum of six weeks. No patient recovering from treated fungal infection has had a relapse.

TABLE 4. *Fungemia in Renal Transplant Recipients*

Patient # Sex Age	Primary Disease	Graft Donor	At Time of Infection		Months to Infection	Fungus	Other Infection Sites	Other Organisms Sites	Treatment	Outcome/Organism
			Serum Creatinine (mg/dl)	Prednisone (mg/day)						
1 F 30	Diabetes	Rel.	2.2	50	2	C. albicans	Urine	CMV† titer rise	Amphotericin-B 5-fluorocytosine	Died—Aspergillus and C. albicans in lungs
2 M 30	Diabetes	Cad.	7.5 dialysis	70	1	C. albicans H. Capsulatum	—	—	Amphotericin-B 5-fluorocytosine	Died—disseminated H. capsulatum and C. albicans
3 M 48	CGN*	Rel.	1.6	20	72	H. Capsulatum	Lung	—	Amphotericine-B	Died—disseminated H. capsulatum, gastric erosions
4 M 52	CGN	Cad.	1.7	45	1	C. albicans	Urine	CMV-titer rise	—	Died—C. albicans, CMV, Klebsiella in lungs, Klebsiella, E. coli—blood
5 M 19	Diabetes	Cad.	6.6	120	2	C. albicans	Urine	Klebsiella urine wound, Pseudomones blood	Amphotericine-B 5-fluorocytosine	
6 F 25	Diabetes	Rel.	2.5	50	5	C. albicans	Urine	CMV-urine, Pseudomonas urine	Amphotericine-B 5-fluorocytosine	Died—Pseudomonas in lungs
7 M 54	Fabry's disease	Rel.	6.8 dialysis	40	1	C. neoformans	—	—	Amphotericine-B 5-fluorocytosine	Transplant nephrectomy; died of cardiac failure 1 yr following 2nd transplant
8 F 28	Diabetes	Rel.	1.4	40	2	C. albicans	Throat	CMV-urine *HVH*‡ throat	Amphotericine-B	Alive
9 M 25	CGN	Rel.	4.2	50	2	C. albicans	Urine	CMV disseminated Staphylococcus blood, Pseudomonas, peritoneum	—	Died—C. albicans, Aspergillus, CMV, Pseudomonas in lungs, necrotic small intestine
10 M 20	Diabetes	Rel.	5.6	30	1	C. albicans	—	Salmonella peritoneum	—	Died—C. albicans in peritoneum, heart, kidney, thyroid

* CGN = chronic glomerulonephritis. † CMV = cytomegalovirus. ‡ *HVH* = *Herpesvirus hominis*.

A newer antifungal agent, 5-fluorocytosine, is effective against Candida and Cryptococcus. Most fungal isolated are sensitive to 5-fluorocytosine before treatment, but because resistant strains develop, amphotericin-B must always be given with 5-fluorocytosine.

Discussion

Renal transplant patients have an increased susceptibility to infections of all types. Fungi, such as Candida, Aspergillus, Torulopsis, and Cryptococcus, are opportunistic invaders that usually cause disease only in the host with altered defenses. Other fungal species, for example Histoplasma, Blastomyces, and Coccidioides are particularly pathogenic, and can cause disease in the uncompromised host as well. *Nocardia* is frequently cited as one of the fungal infections.[5-7] Although it has a hyphal-like growth pattern, Nocardia is a true bacterium and was not considered in this paper. In fact, no Nocardia infections were encountered in our patients who were generally maintained on sulfisoxasole prophylaxis.

Most reported fungal infections in renal transplant recipients have been of the opportunistic variety. Rifkind, et al.[15] were the first to review systemic fungal infections in a series of transplant patients. They found systemic fungal infections in 23 of 51 autopsy reports; only one case was recognized before death. Concurrent bacterial, viral, or parasitic infections were present 87% of the time. Such combined infections are still the rule in transplant patients who die with fungal infections. Death, however, can be the result of isolated fungal infections.

Since Rifkind's initial report, an high incidence of fungal infection has been noted by kidney, heart, and liver transplant groups.[3,5-7,10,11,16,17,19,23,26,27] Almost all agree that the risk factors in transplant patients include the use of large doses of corticosteroids, multiple or recent rejection episodes, hyperglycemia, poor transplant function, leukopenia, and older age. In general, men seem to be more susceptible.[15]

Not all reports agree that each of these predisposing factors is important. For example, our data suggest that diabetics, patients with poor renal function, previous rejections, or recent courses of high dose steroid therapy were more susceptible to lethal infections which followed their initial bacterial or viral infections. Rifkind, however, could find no positive correlation with steroid-induced diabetes, leukopenia, hypogammaglobulinemia or antibiotic administration. Gallis, et al.[5] found no relationship with leukopenia or renal function.

Previous reports in this area have been of two types: The first includes a general survey of fungal infections.[5,7,15,17,27] In these studies the common fungi observed are Cryptococcus,[16] Candida,[5] and Aspergillus,[5,6] with occasional reports of Phycomyces, Chromomyces or soft tissue infections with *Phialophora gougeroti*.[5] The central nervous system, lung and blood were the most frequently affected. A second type of report describes infections with specific fungus in transplant recipients.[3,6,11,16,19,26,27] Many of these reports assume that a source of Candida infection is frequently present and may serve as a reservoir for later or concomitant systemic infection.

For some time, we[9,20-25] have been interested in the clinical pattern of certain infectious diseases in immunosuppressed transplant patients. The recognition of such clinical patterns could help provide an early, therapeutically essential, diagnosis of these patients. From this point of view, it becomes clear that Candida is commonly a surface contaminant in the nose, throat, urine, and open wounds of transplant patients, and that these infections seldom act as a reservoir of systemic infection. Nevertheless, the potential of reservoirs for systemic infection is real.[28] Table 1, while demonstrating that a large number of kidney recipients have reservoirs of fungi, does not provide a true incidence of fungi in superficial sites because the entire transplant population was not evaluated. We must conclude, therefore, that all transplant patients seem to have fungal reservoirs and that the high incidence of patients with Candida in superficial sites is not a great cause for concern.

Clinical infections caused by fungi appear to fall into two groups. The first group of infections occur early during the first six months after transplantation when acute rejection is at most risk. Because these patients receive large doses of steroids, they are susceptible to infections of all types. Fungemia is almost always found in patients who have concomitant infections. Our past reluctance to use systemic antifungal agents in patients with mixed infection may contribute to the lethal outcome of systemic life-threatening infections. We are currently attempting to counteract this tendency by instituting systemic treatment with amphotericin-B (usually in conjunction with 5-fluorocytosine) in patients with systemic infections, with known viruses and bacteria, who do not respond to appropriate treatment. Because fungi grow slowly in culture, concomitant fungal infections are sometimes not recognized until too late.

In the second group of fungal infections the fungus is the primary infecting agent. These infections occur in the central nervous system, in the lung or as a rare appearance of sudden fungemia years after transplantation. Such patients most frequently have had multiple rejection episodes or mild impairment of renal function, and may have had previous multiple infections of other types. We take an aggressive attitude towards all symptoms of central nervous system involvement. We perform spinal taps and do India ink preparations, and culture the spinal fluid in all cases. Recently we have also been performing fungal serology on the spinal fluid. This serologic technique is especially helpful for cryptococcal infections. Similarly, patients who appear with infiltrates of the pulmonary parenchyma usually are bronchoscoped on the day of admission so that a prompt fungal or bacterial etiology can be determined. Primary central nervous system fungal infections and primary pulmonary infections are seldom lethal, even though these patients may die later from other infectious agents. As stated previously, patients who develop bacterial and viral infections are frequently the most susceptible to subsequent fungal superinfection.[21] In such a case serious consideration should be given to reducing immunosuppressive therapy or even sacrificing the kidney graft.

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Use of the Stomach as an Esophageal Substitute

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Esophagoplasty with isoperistaltic stomach is a useful and satisfactory means of reconstruction of the esophagus. It is simpler and there is no necessity for using a reversed gastric tube. The most essential points of technique for the modelling of the stomach, is taking advantage of the ample intramural vascular network and adequate selection of the highest point of the stomach for the site of the esophago-or pharyngogastrostomy. To utilize the intramural vascular network, sufficient width of the stomach is necessary. This also allows strecthing of the stomach. Esophageal resection and reconstruction using the isoperistaltic stomach above the level of the neck was performed on 130 cases. Among them 40 cases were pharyngogastromies and 90 cases were cervical esophagogastromies. There was one operative death due to alcoholic liver cirrhosis (operative mortality rate 0.8%). If the stomach is properly handled, esophageal replacement by the isoperistaltic stomach gives constant success.

THE COLON AND THE STOMACH are the most common organs used to replace the esophagus. Each organ has its own advantages as a substitute for the esophagus, however, the stomach is more advantageous for its simplicity when properly used. This report emphasizes the use of the stomach in simple isoperistaltic fashion and describes the technical details of handling the stomach based on anatomical considerations. This is essential to achieve constant success in esophageal reconstruction at any level.

Materials

From October, 1972 to October, 1977, 340 cases of various esophageal lesions including those of the hypopharynx and esophagogastric junction were admitted to the Department of Surgery at the Toranomon Hospital. A total of 269 reconstructive procedures of the esophagus, including bypass procedures were performed. Resection and reconstruction were carried out in 228 cases. After resection of the thoracic or entire esophagus, esophageal reconstruction with the anastomosis in the neck was completed with the stomach *via* a retrosternal route or the posterior mediastinal route in 130 cases. This paper is based on an analysis of these 130 cases.

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Operative Technique

Position of Patient and Skin Incision

The patient is placed supine for reconstruction of the esophagus. The front aspect of the entire neck, chest and abdomen is prepared and draped. The abdominal incision is upper midline. The cervical incision is placed either transversely above the left clavicle for cervical esophagogastrostomy or U shaped for pharyngogastrostomy.

Principles of Utilization of the Stomach

Whether the stomach can be used for esophageal substitution or not, depends solely on technique based on anatomical reasons unless the stomach has an anomalous vascular pattern or is extremely small in size which is rather unusual.

The Principles of use of the stomach are as follows. 1) Use in simple isoperistaltic fashion. 2) Resection of the proximal half of the lesser curvature so as to remove possible lymphatic spread in malignant lesions of the esophagus. 3) A reasonable preservation of intramural vascular network. 4) Take advantage of its large size and stretchability.

Use in simple isoperistaltic fashion. When the stomach is used as an esophageal substitute, the most important vessels are the right gastroepiploic and the right gastric arteries and veins.[5,7]

After opening the omental bursa, the full course of the right gastroepiploic artery is preserved until it gives the last branch to the greater curvature of the stomach (Fig. 1). It is severed at the point where it goes into the stem of the left gastroepiploic artery. Excessive omentum should not be retained. All the short gastric vessels are divided. The greater curvature is freed until the abdominal esophagus is exposed. The posterior gastric artery arising directly from the splenic artery as the first branch of the short gastric arteries, is also severed.

Lesser curvature. The method of handling the lesser curvature of stomach depends on whether the primary

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Submitted for publication: February 21, 1978.

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esophageal lesion is benign or malignant, and also whether the lesion is located in the thoracic esophagus or in the neck.

When the primary lesion is carcinoma of the thoracic esophagus, lymph node dissection around the cardia, proximal half of the lesser curvature, celiac axis and common hepatic artery is mandatory. This necessitates severance of the left gastric artery at its root and resection of approximately the proximal half of the lesser curvature and the cardia of the stomach (Figs. 1 and 2i). Resection of the proximal half of the lesser curvature should include the first, second and third proximal brances of the left gastric artery, so as to remove lymph node spread to this area. This is recommended because an analysis of lymph node spread shows that there is a decreasing positivity of lymph node involvement such that the nodes along the first branch of the left gastric are more often positive for tumour than those along the second branch. The nodes along the third branches have always been negative for tumour spread. Consequently, the antral portion of the right gastric artery is preserved. It is rather rare to find lymph node involvement in the suprapyloric region and on the greater curvature of the stomach.

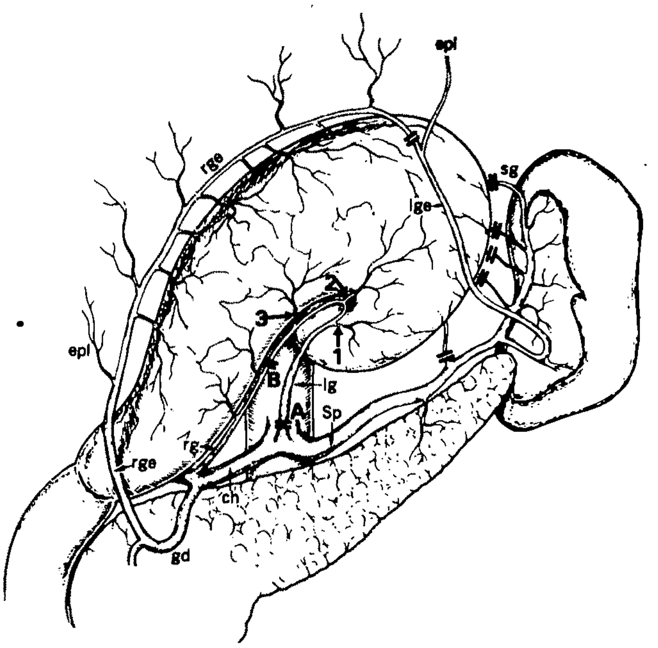

FIG. 1. Main arteries of the stomach and points to sever for esophageal substitution. Posterior view of the stomach through the opened omental brusa. When the proximal lesser curvature and cardia are resected, the left and right gastric arteries are severed at the points A and B respectively. When the whole stomach is used, the left gastric artery is severed at its root (A), and the whole length of the arterial arcade of the lesser curvature is preserved. Key: rge: rt. gastroepiploic; lge: lt. gastroepiploic; epl: epiploic; rg: rt. gastric; lg: lt. gastric, sp: splenic; sg: short gastric; ch: common hepatic; gd: gastroduodenal; 1,2,3: 1st, 2nd, 3rd branches of the left gastric artery to the cardia and proximal portion of the lesser curvature. =: point to sever.

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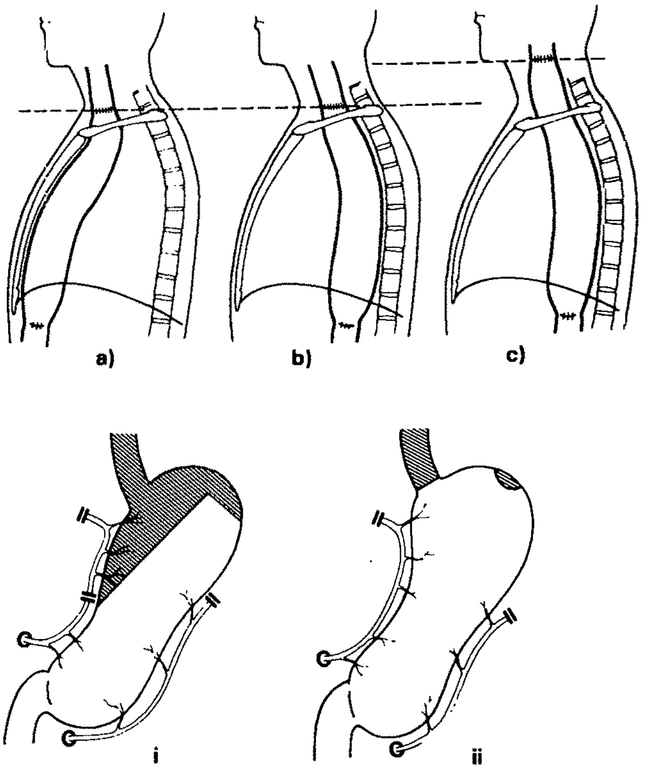

FIG. 2. Routes of reconstruction and two basic methods of use of the stomach. (a) retrosternal route, anastomosis at cervical level. (b) posterior mediastinal route, anastomosis at cervical level. (c) posterior mediastinal route, anastomosis at pharyngeal level. (i) The stomach after resection of the cardia and approximately the proximal half of the lesser curvature. (ii) The whole stomach with the full length of the vascular arcade on the lesser curvature preserved.

When it is not necessary to consider intra-abdominal lymph nodes metastases such as in hypopharyngeal carcinoma and benign stricture, the whole length of the arterial arcade on the lesser curvature is preserved (Figs. 1 and 2ii) and the whole stomach is preserved. In some cases as the lesser curvature is extremely short due to shortening of the arterial arcade, the right gastric artery must be cut at an appropriate point and an area of the lesser curvature and cardia resected to unload the vascular pedicles, so as to obtain a better blood supply. This procedure is also useful in order to maintain sufficient blood supply into the rest of the stomach, particularly when the communicating arcade between the right and left gastric artery is poor. The stomach prepared as described above can be utilized as an esophageal substitute to any level of anastomosis through the retrosternal or posterior mediastinal route (Figs. 2a–c).

Preservation of intramural vascular network. The stomach is an organ which has an ample intramural arterial anastomosis as well as venous. It is an extremely important point of technique to tailor the stomach so that the vascular network is effectively preserved to

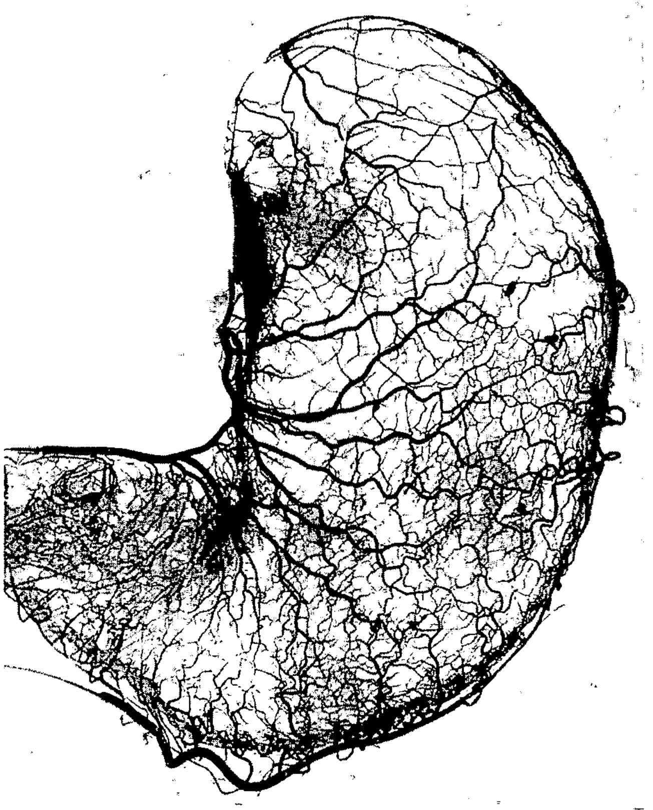

FIG. 3. Arteriogram of the stomach (whole stomach). The whole stomach prepared as Figure 2ii. Extensive arterial network is seen. Dye is injected only from the right gastric and gastroepiploic arteries.

maintain good blood supply at the proposed area of anastomosis. Figure 3 is an arteriogram of the normal gastric wall in a full size stomach taken from a cadaver and prepared as Figure 2ii. Contrast media of barium was injected from both the right gastric and gastroepiploic arteries with all other vessels ligated. The left gastric artery is cut and ligated at its root and its cardiac branches are left open through the arterial arcade of the lesser curvature. The intensive intramutal arterial network with multiple anastomoses between the arterial arcades of lesser and greater curvature is well visualized (Fig. 3). This abundant vascular network is also recognized in the venous system by transillumination of the gastric wall done by fibergastroscopy. The intramural vascular network must also be preserved after resection of the proximal half of the lesser curvature and cardia of the stomach as in Figure 2i. For this purpose, sufficient width of the stomach must be maintained. Figure 4 is an arteriogram of the stomach which was taken from a cadaver and prepared in such a fashion. Well preserved intramural vascular anastomosis are observed and sufficient arterial supply is noted at the top of the stomach.

The extent of resection of the lesser curvature is determined by the line connecting the points where the vessels of the lesser curvature enter the stomach wall (Fig. 5). By this procedure lymph nodes along the vessels are all removed and most of the intramural vascular network and anastomoses with ascending branches to the fundus are kept intact. Then the stomach proximal to the last arterial branch of the right gastroepiploic artery has sufficient blood supply for the anastomosis. Care must be taken not to traumatize the venous system so as to maintain normal venous return.

To take advantage of its large size and stretchability. It is wise to make the most of the stretchability of the stomach. This is related to correct selection of the highest point of the stomach. By pinching up the stomach with the fingers and raising it, the highest point is chosen for the area of the anastomosis for pharyngogastrostomy or cervical esophagogastrostomy. Applying counter traction between the highest point and the point on the lesser curvature where the arterial arcade is severed, the cardiac portion of the stomach including the proximal half of the lesser curvature is resected by stapler. As stated above, the width of the rest of the stomach should not be too narrow because the intramural vascular network must be preserved. Maintaining width also helps to elongate the residual stomach (Fig. 5). The cut ends of the right gastric and gastroepiploric arteries and veins are tacked to the gastric

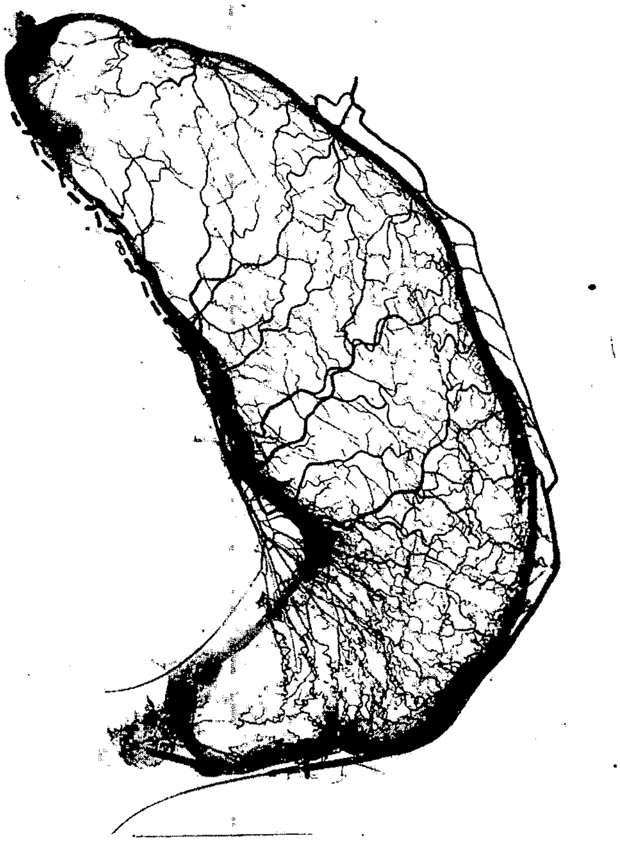

FIG. 4. Arteriogram of the stomach (after cardia and proximal lesser curvature resection). The stomach prepared as Figure 2i. Intramural arterial network is sufficiently seen even after resection of the cardia and the proximal half of the lesser curvature.

wall to prevent tearing of the vessels during elevation of the stomach through the retrosternal or posterior mediastinal tunnel. Kocher's maneuver is added when it is thought necessary. Pylorplasty is routinely performed.

Creation of Retrosternal Tunnel

The head is slightly rotated to the right to approach the cervical esophagus through the left side of the neck. A small skin incision is placed transversely 2 cm above the head of the left clavicle. This incision is satisfactory also for cosmetic appearance.

After securing the retrosternal space through the neck and the abdominal incision, a maleable intestinal retractor[3,5] is inserted into the anterior mediastinum sliding the tip of the retractor close to the posterior surface of the sternum and not deviating from the midline. In order to obtain a wide opening of the superior aperture of the mediastinum, transection of the sternohyoid and sternothyroid muscles is necessary and the width of the retrosternal tunnel is extended laterally to get more space behind the medial half of the left clavicle. This secures a wider opening of the top end of the tunnel. There is no difficulty in bringing the stomach up to the neck through the retrosternal tunnel. The stomach is slightly rotated so that the suture line on the lesser curvature lies posteriorly and therefore is incorporated into the posterior wall of the anastomosis, thus preventing leakage.

Creation of Posterior Mediastinal Tunnel

For lesions of the hypopharynx, the thoracic esophagus is bluntly resected by various means such as the fingers or eversion stripping by a vein stripper, and the posterior mediastinal tunnel is created.[1,4,8,9,11] Usually the whole stomach is brought up to the hypopharynx through this tunnel. The esophageal bed after resection of the thoracic esophagus through a thoracotomy may also be used as the route of esophageal reconstruction. However this is not recommended when the resection is incomplete.

Esophageal Anastomosis

The anastomosis between the esophagus or hypopharynx and the stomach is performed in two layers with 5-0 silk or with an absorbable fine suture material with low tissue reaction. As reported,[2] the most accurate approximation of edge of mucosa to edge of mucosa with layer to layer anastomosis is essential for primary healing of the anastomosis. Figure 6 shows the completion of esophagogastrostomy and pharyngogastrostomy.

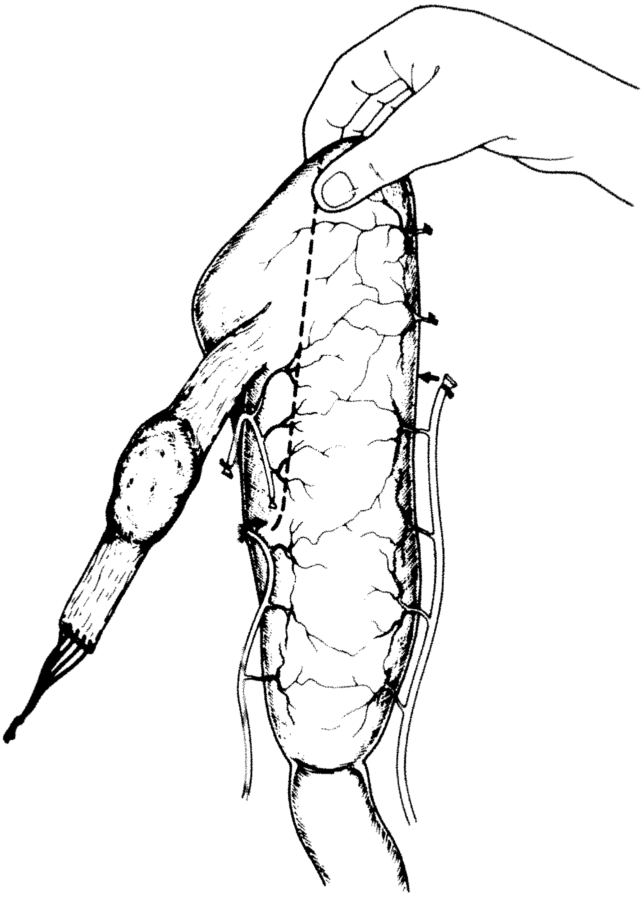

FIG. 5. Selection of the highest point of the stomach by "pinching-up" with the fingers. This is a simple maneuver, but essential to obtain satisfactory esophageal substitute. When the cardia and proximal lesser curvature are resected, staplers are placed on the dotted line. This line is connecting the points where the vessels of the lesser curvature enter the gastric wall. Cut ends of the vessels are tacked to the gastric wall (Arrow).

Results

Among 228 cases who underwent resection and reconstruction of the esophagus or hypopharynx, 130 cases utilized the stomach with anastomosis in the neck, with one operative motality on the thirty first postoperative day due to alcoholic liver cirrhosis with uncontrollable ascites. Leakage of the anastomosis was noted in six cases (4.6%) including minor ones. One of them developed in a moderately severe diabetic patient, one in a case with extremely short stomach and three in cases with intensively irradiadiated skin of the neck and all of them healed spontaneously. As shown in Table 1, this operative procedure has proven to be a safe and satisfactory method of reconstructing the esophagus. Since this paper is purely focussed on the surgical technique, studies on long-term results in relation with combined therapy will be separately discussed.

Comments

One of the most common methods of esophageal reconstruction or bypass is that of using the colon. While esophagoplasty with the colon contains three anastomoses, that with isoperistaltic stomach is completed with only one anastomosis. Esophagoplasty with

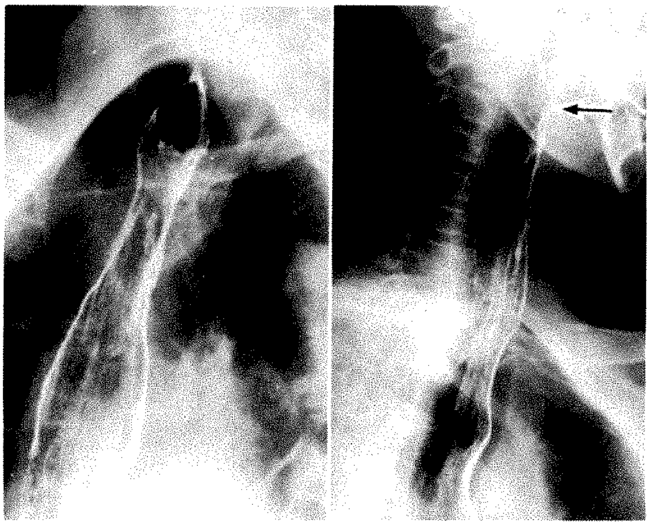

FIG. 6. Postoperative barium swallow after esophageal reconstruction using the stomach. (a, left) Cervical esophagogastrostomy (arrow), retrosternal route. (b, right) Pharyngogastrostomy (arrow), posterior mediastinal route.

stomach has enjoyed more popularity as reversed gastric tube[6] rather than the isoperistaltic stomach. However, the advantage of the isoperistaltic stomach has not been emphasized. This might be due to the fact that it has been thought that the isoperistaltic stomach is not long enough to replace the esophagus. It is well known that the stomach is large enough to reach the hypopharynx.[1,4,8,9] For carcinoma of the thoracic esophagus, it is mandatory to resect the cardia and the upper half of the lesser curvature for removal of the lymph nodes in that area. This is sometimes neglected when the reversed gastric tube is used. The stomach still has sufficient length for esophageal substitution even after cardiectomy. However, to obtain successful results, careful attention to detail in technique is necessary.

The main vascular pedicles for the isoperistaltic stomach are the right gastric and gastroepiploic arteries and veins. Besides this the importance of preservation of the intramural vascular network to the anastomosis has not been described. Although a plastic procedure on the stomach creating the so-called isoperistaltic "gastric tube" along the greater curvature with rather narrow width,[10] provides the longest tube it also destroys all the intramural vascular network resulting in impaired blood circulation at the tip of the gastric tube. Thus, width is an important factor in making a satisfactory esophageal substitute. Another point in using the stomach properly is to select the top point of the stomach in its extended position with the aid of its extensibility.

TABLE 1. *Resection and Reconstruction Using the Stomach in One Stage with Anastomoses at the Pharyngeal and Cervical Levels*

Level of Anastomoses	Route of Reconstruction: Retrosternal	Route of Reconstruction: Posterior Mediastinum	Total	Operative Death
Pharyngeal level	0	40	40	0
Cervical level	83	7	90	1
Total	83	47	130	1 (0.8%)

Toranomon Hospital, Oct. 1972–Oct. 1977.

The technique is not very complicated. A little thought is required before the stomach is cut. There is no difficulty in using the simple isoperistaltic stomach for esophageal replacement and there seems to be no need for creating a reversed gastric tube. The method of esophageal replacement is closely related to the primary lesion of the esophagus. In cases such as carcinoma of the thoracic esophagus, the cardia and lesser curvature must be resected. In other cases, such as carcinoma of the hypopharynx, the whole stomach may be used.

The retrosternal route is convenient for the former. The posterior mediastinal route after resection of the esophagus may also be used, but only when the resection is complete. For anastomosis at the pharyngeal level, the posterior mediastinal route is superior, because of the three routes, the posterior mediastinal route is shortest. The subcutaneous route is the longest and presents a cosmetic problem. The retrosternal route is longer than the posterior mediastinal route but has various advantages.[5]

Acknowledgment

The authors are grateful to Dr. Michio Inui, Chief, Tokyo Metropolitan Medical Examiner's Office for his assistance in handling the stomach.

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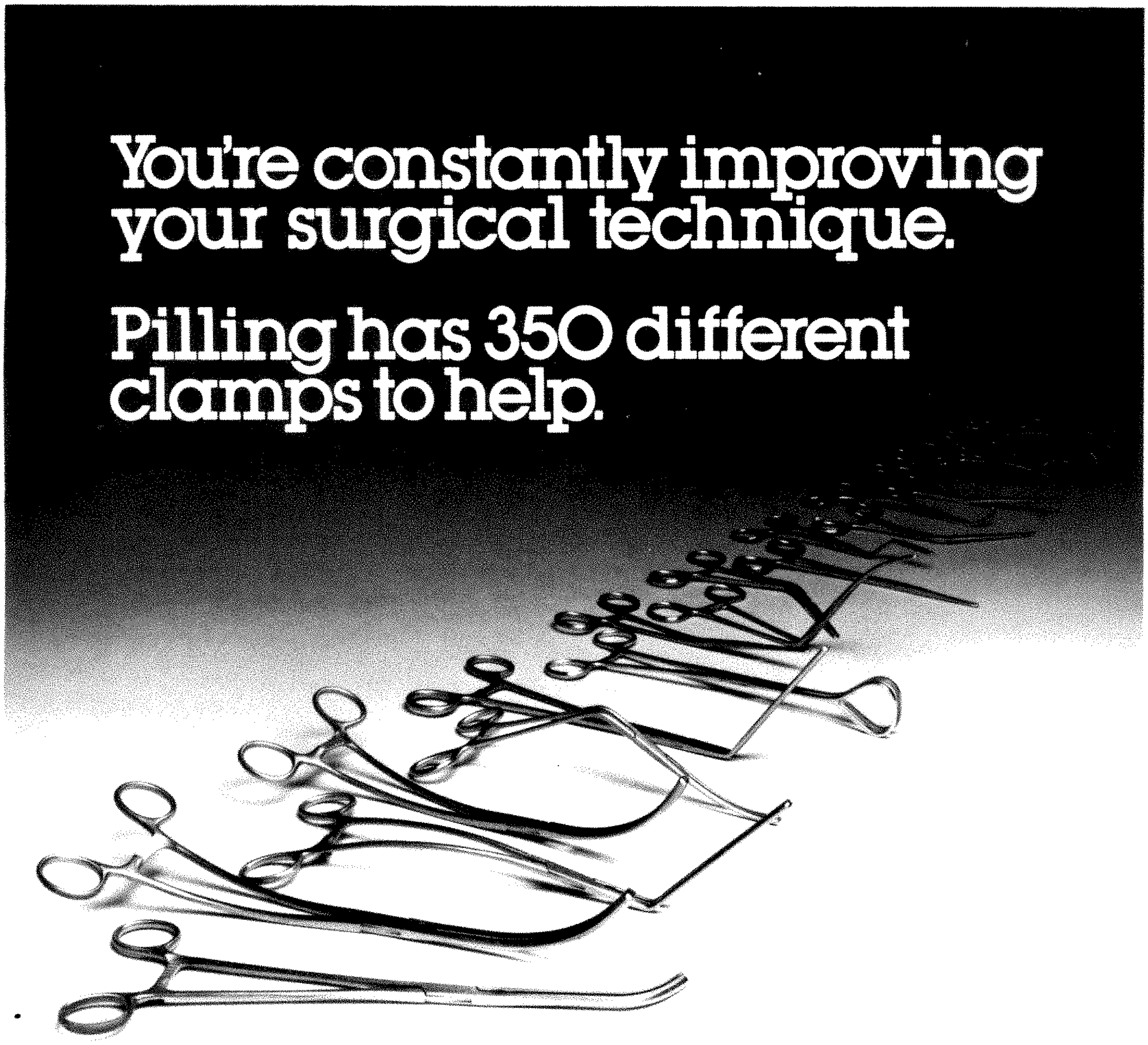
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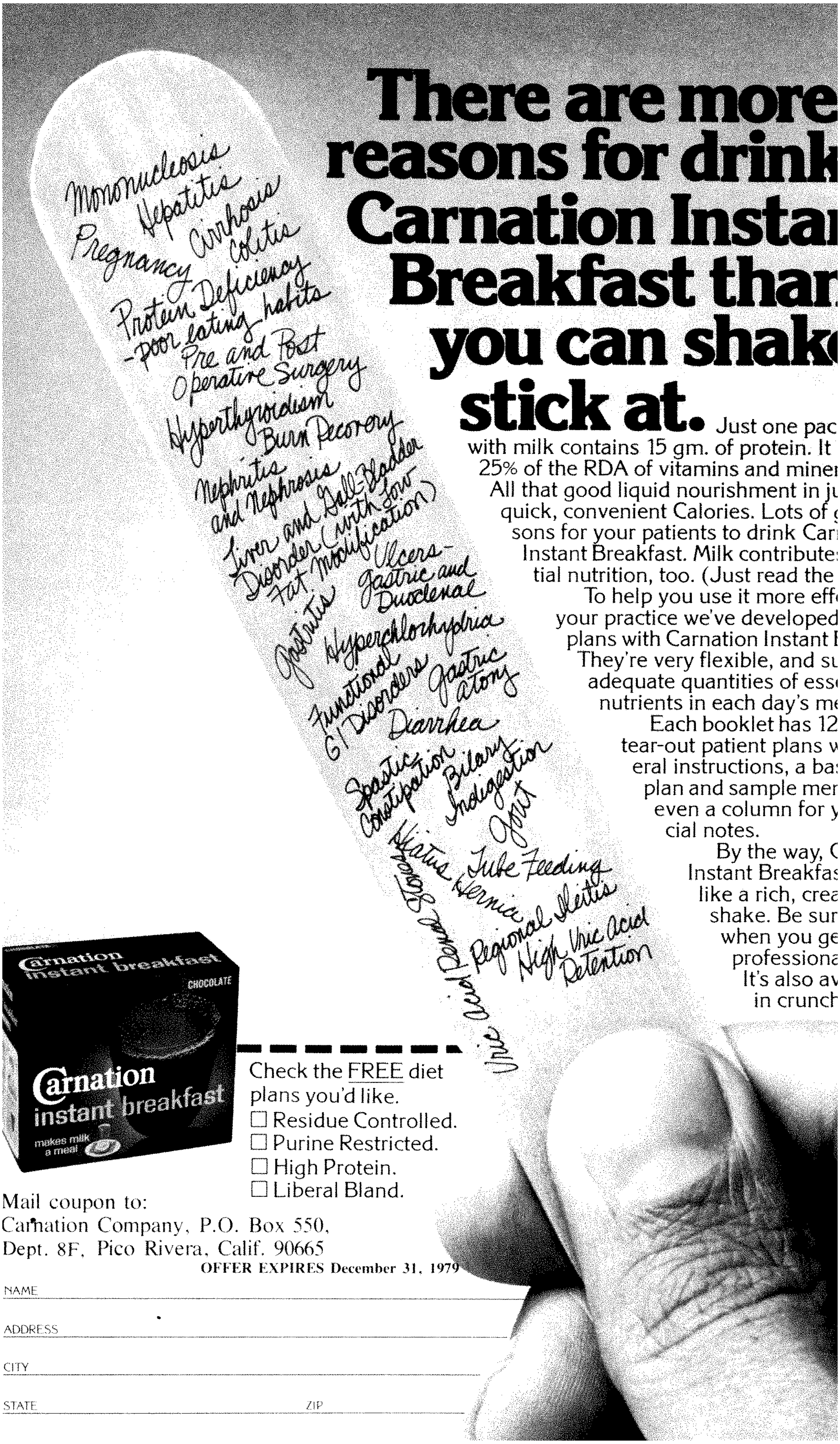

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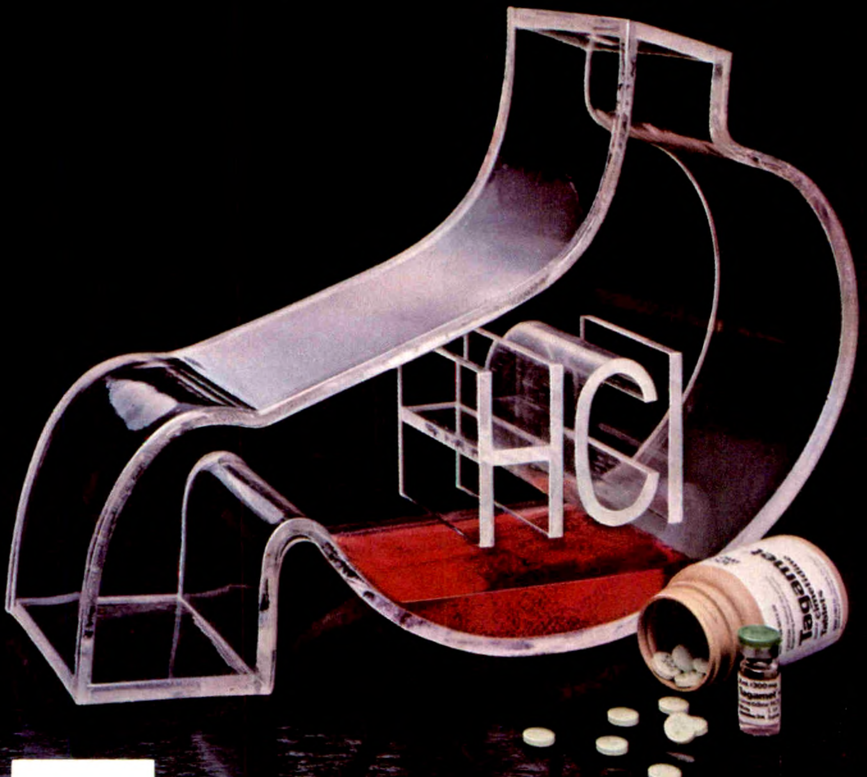

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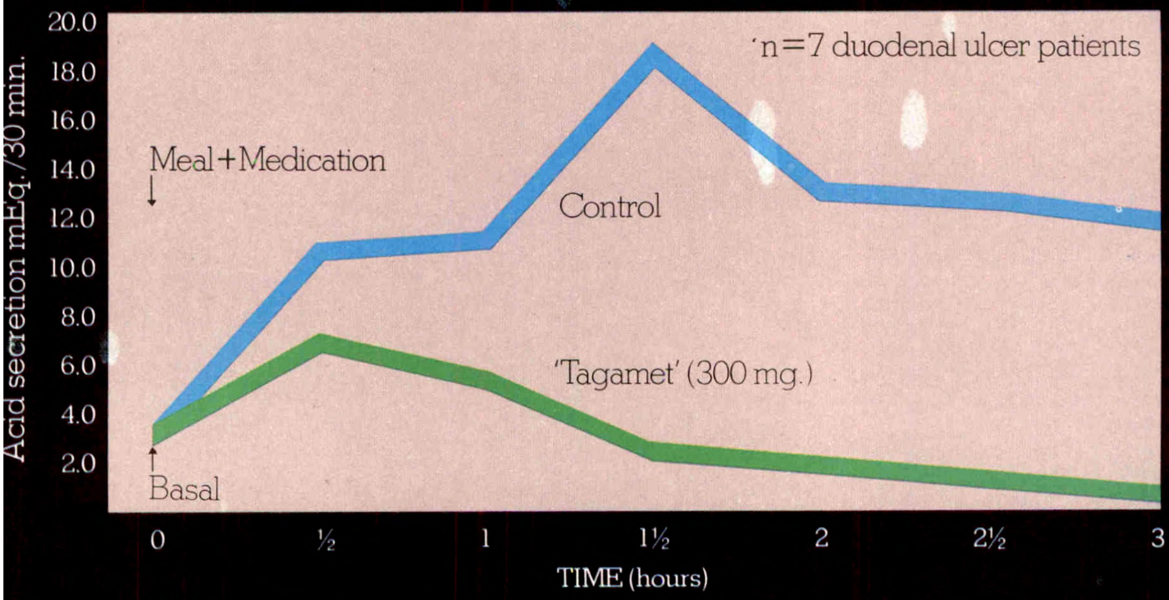

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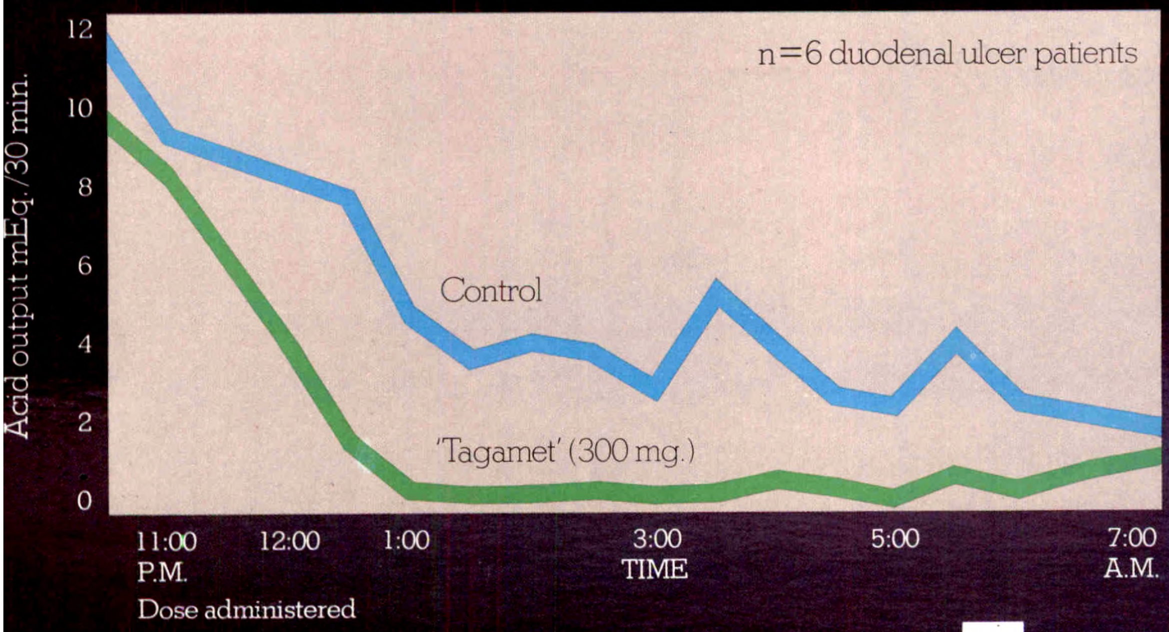

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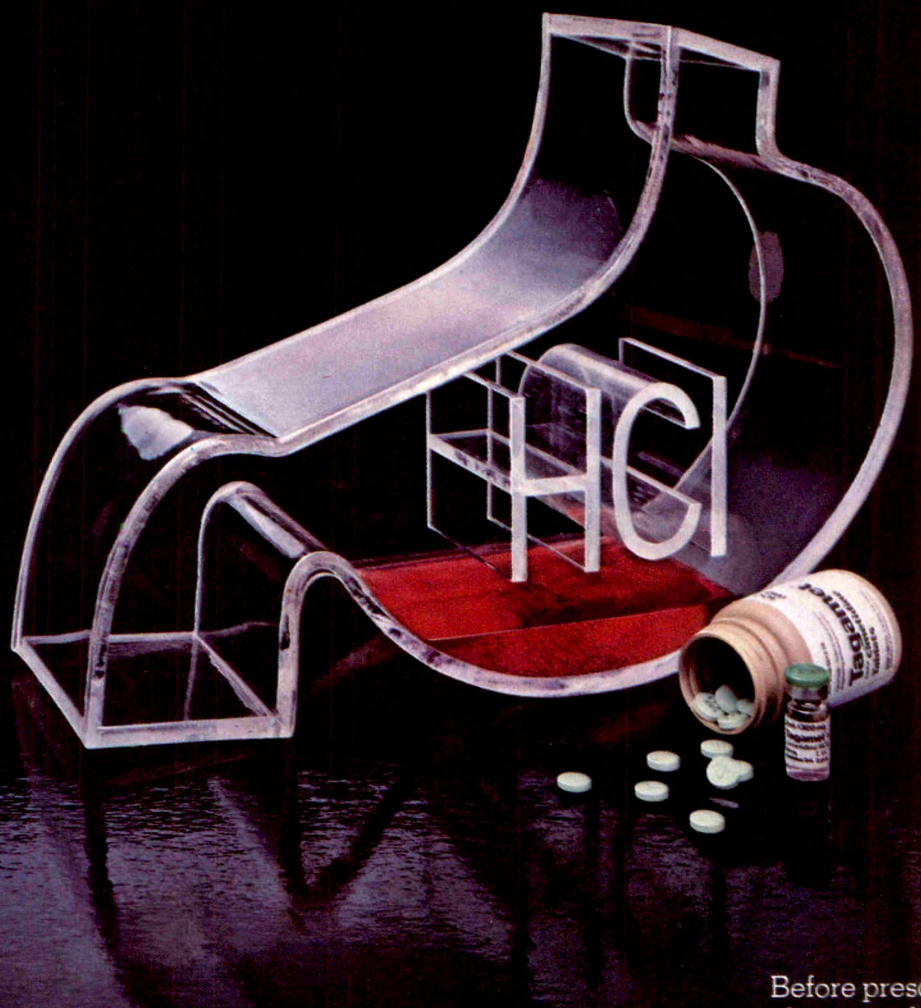

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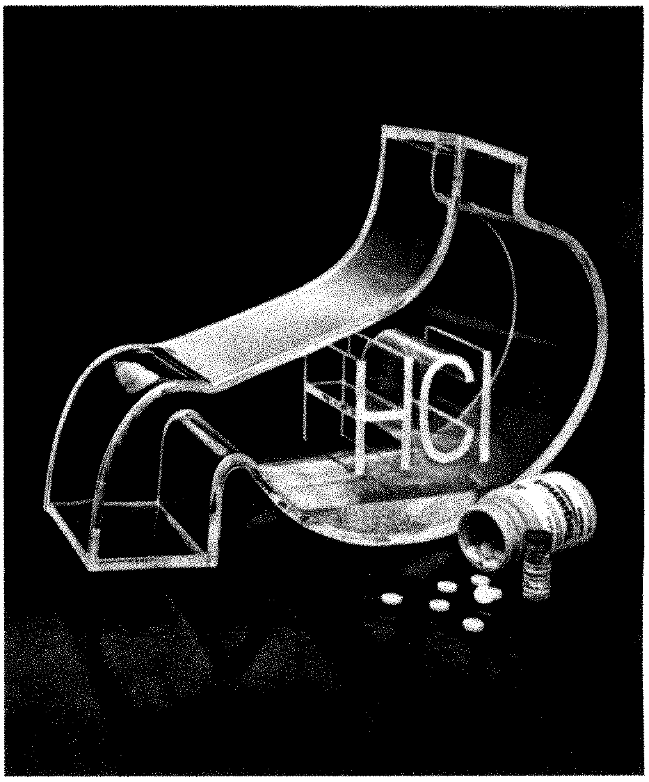

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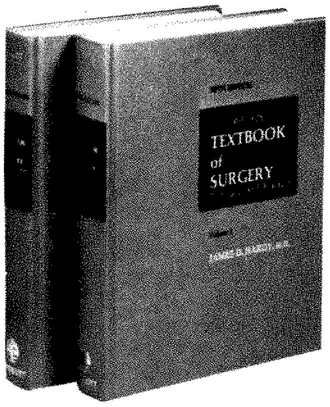

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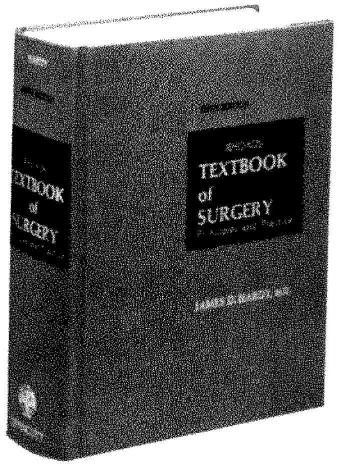

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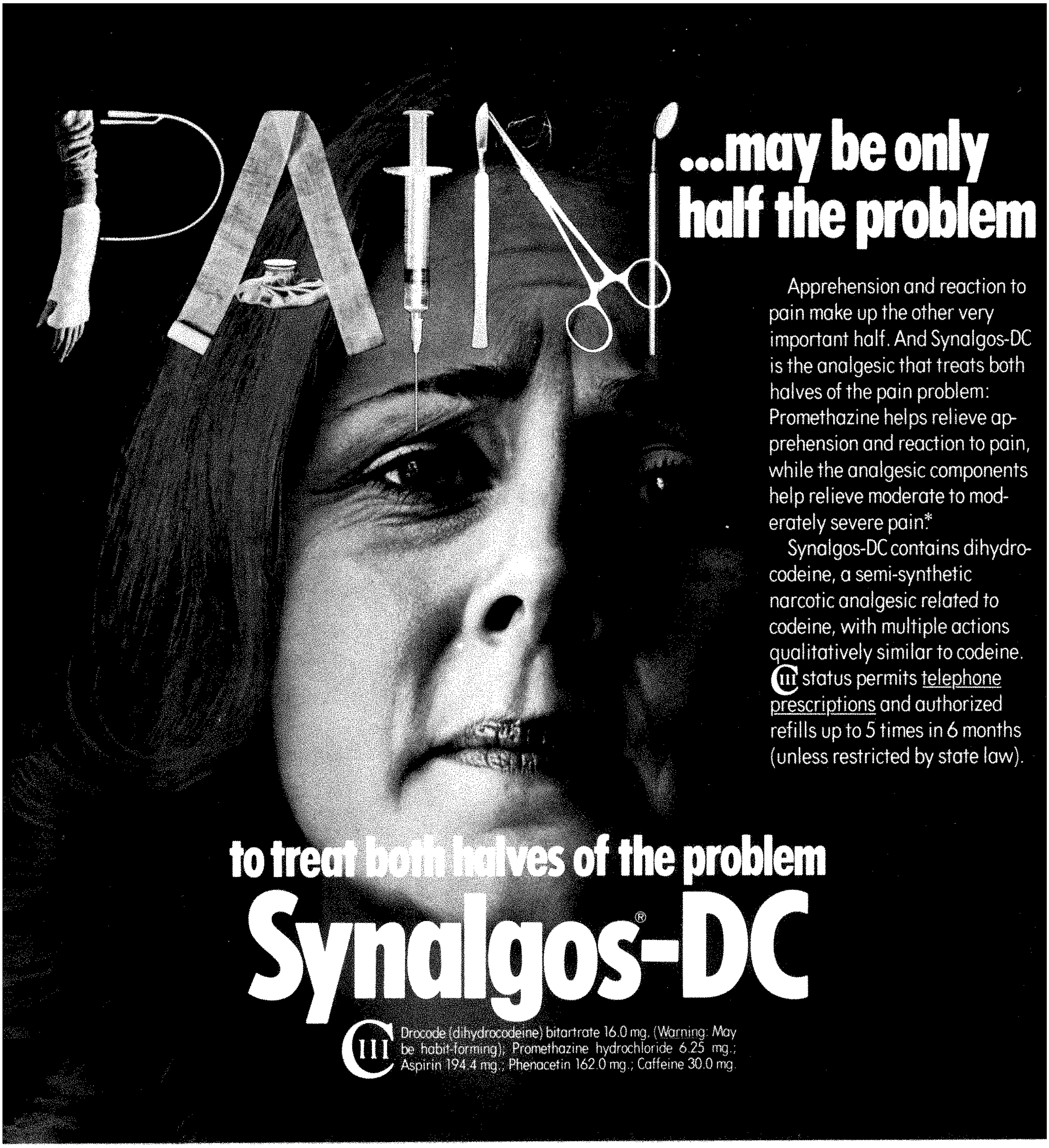
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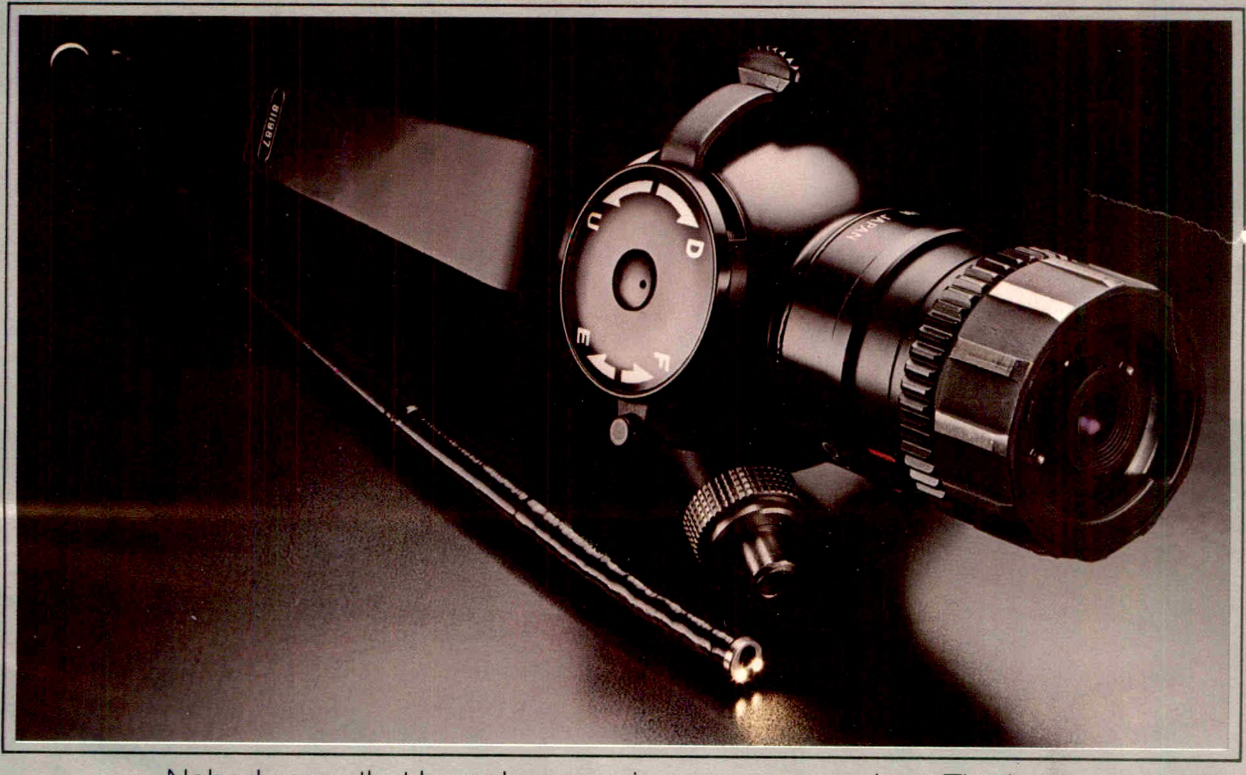

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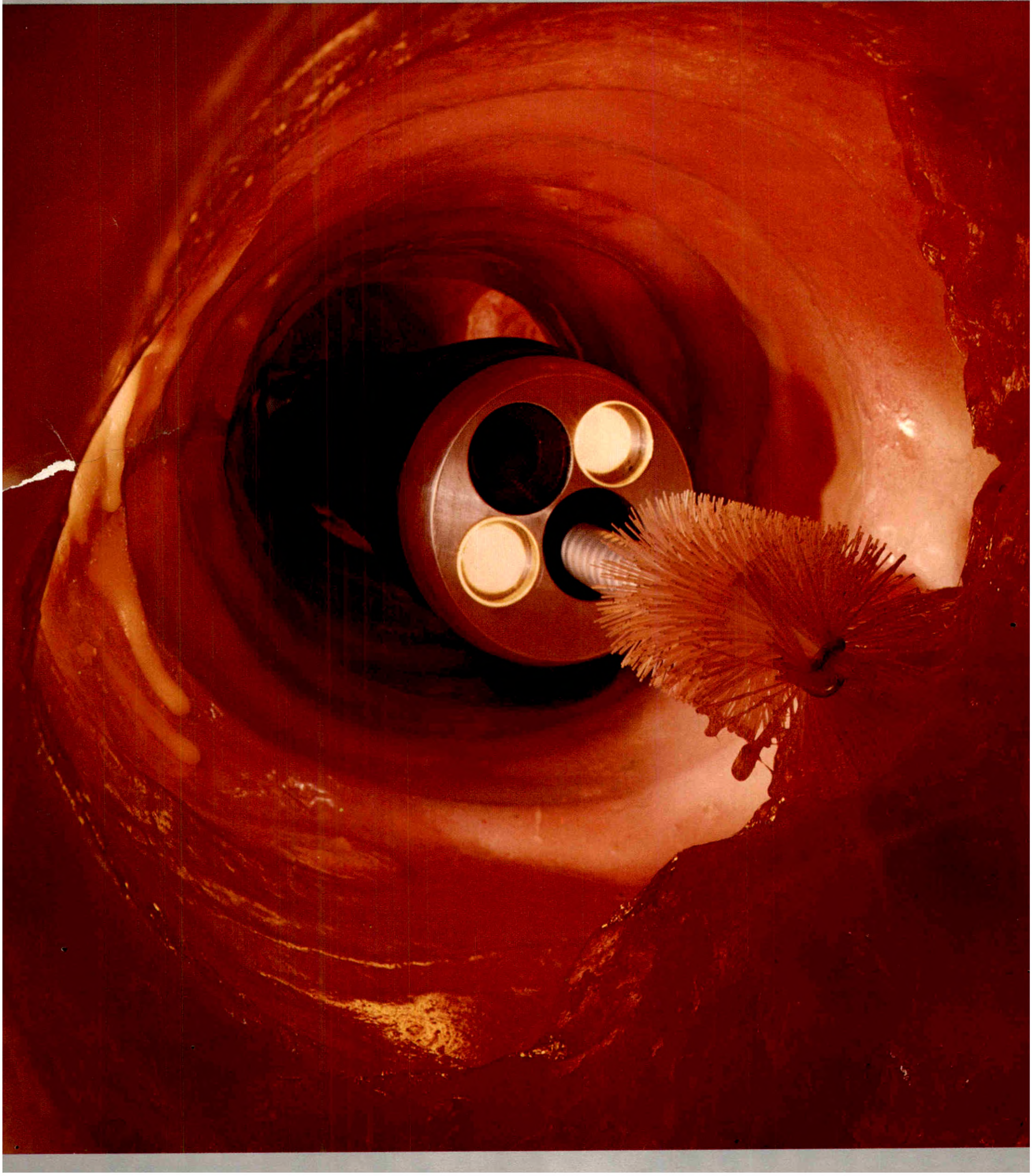

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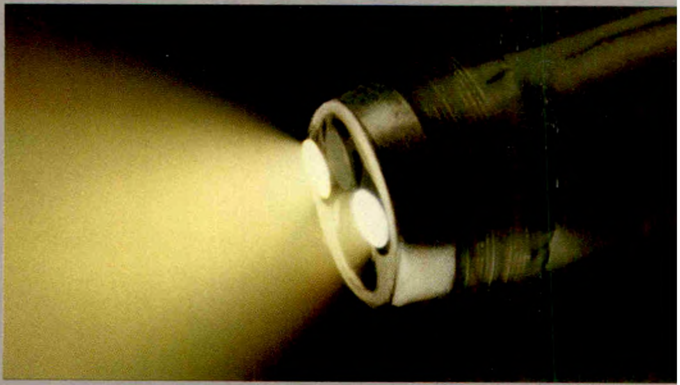

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The Preclotting of Porous Arterial Prostheses

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A four-step preclotting method is presented for use with porous filamentous Dacron® prostheses in the fully-heparinized patient. The method employs controlled fibrin formation within graft interstices, heparin neutralization of all thrombin remaining in the graft wall, and delay of systemic heparin neutralization until 15–20 minutes after clamp release. The resulting flow surface is impervious, smooth and hypothrombogenic. Experimental data are presented which support the rationale of this four-step preclotting method. Four years of clinical experience with the method are summarized, involving 300 prosthesis limbs used in aortic bifurcation, aortofemoral, femorofemoral, axillary-femoral and femoropopliteal positions in 192 patients. A clinical perspective of preclotting techniques is presented in which the proper use of this new method is suggested.

From the Reconstructive Cardiovascular Research Center, Providence Medical Center and The Department of Surgery, School of Medicine, University of Washington, Seattle, Washington

THE WALL OF AN ARTERIAL PROSTHESIS must be porous if the body is to heal it. But fabric prostheses porous enough to be healed will bleed excessively at operation unless the walls are rendered impervious by preclotting. "Preclotting" refers to the conversion of the porous wall of a fabric prosthesis into one which has been rendered impervious by reaction with blood. The preclotting process is absolutely essential if porous fabric prostheses are to be employed in heparinized patients. Preclotting is also important when such grafts are used in nonheparinized patients. In view of this, we find it surprising that little study has been given to the subject.[4,10,14,15,35]

Three methods of preclotting are in common clinical use today. The first method involves submersion of the prosthesis in a pan of blood where it is left until solid clotting occurs. In the second method, termed "*in situ*" preclotting, the graft is wetted with blood to initiate fibrin formation in the interstices. This partially preclotted graft is then anastomosed to the proximal host vessel after which the arterial clamp is intermittently opened, allowing blood to pulse into the graft, permeate the interstices and complete the preclotting process. The third method, a variant of the second, is to proceed as just described but without prior wetting of the prosthesis by blood. All these methods share three serious disadvantages: none makes the graft adequately impervious for use in the fully-heparinized patient, the flow surface of the graft is not necessarily made smooth, and this surface is highly thrombogenic.

Because of dissatisfaction with these limitations we developed a preclotting method to eliminate them. It has four key steps and is termed the "four-step preclotting method." This technique was evolved during the period 1968–1973. It has been used in standardized form since January, 1974, and has been proven to give a flow surface that is impervious, smooth and hypothrombogenic. This method has permitted us to use the USCI® Sauvage ™ Filamentous Vascular Prosthesis*[26–32,36] safely in the fully-heparinized patient. In addition, as the graft is impervious, we can delay neutralization of heparin with protamine sulfate for 15–20 minutes after the clamps have been removed and full flow established. We delay administration of protamine sulfate because our experimental studies (*vide infra*) show that this delay in heparin neutralization significantly improves the one week patency rate of 4 mm prosthetic grafts of this type* in the canine carotid artery.

In this paper we describe the four-step preclotting method, present pertinent experimental and clinical data, and offer a clinical perspective of preclotting which we hope will be useful to the clinical surgeon.

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Submitted for publication: March 1, 1978.

* The USCI® Sauvage ™ Filamentous Vascular Prosthesis (USCI, A Division of C. R. Bard, Inc., Billerica, Massachusetts), constructed of fully-texturized Dacron® yarn, is a highly porous graft to which a velour component has been added, giving full-wall filamentousness of a differential degree, maximal outside and minimal inside. The prosthesis has a wall thickness including the velour of 0.5 mm and has a water porosity averaging approximately 2,000 ml/cm²/min at 120 mm Hg.

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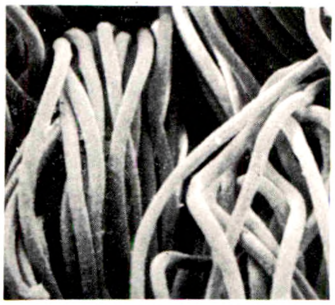
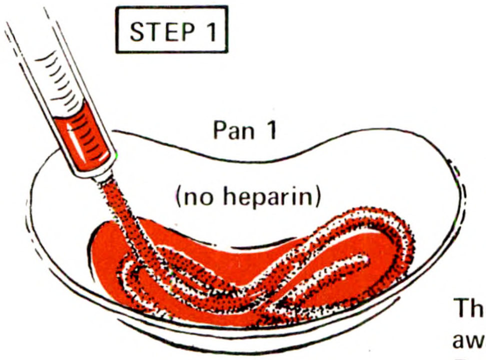


SCANNING ELECTRON MICROPHOTOGRAPH (SEM) of USCI®
SAUVAGE™ FILAMENTOUS VASCULAR PROSTHESIS, x200.
Inner surface of virgin prosthesis before preclotting.

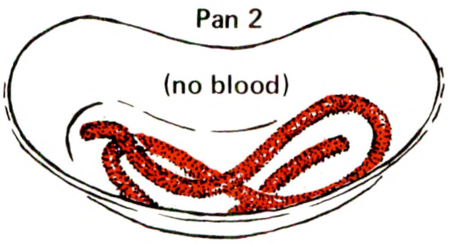
FOUR-STEP PRECLOTTING METHOD

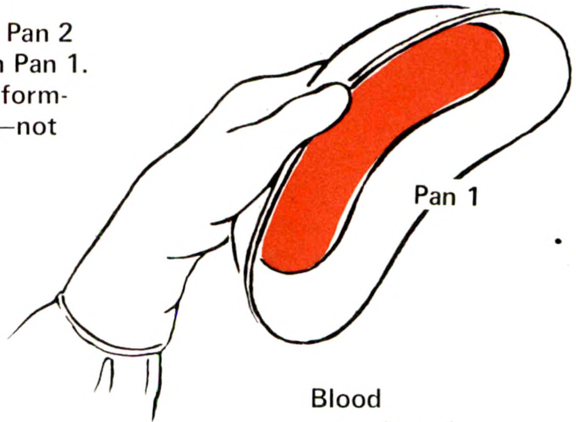
To avoid repeated venipunctures, insert needle with attached stopcock into vein in operative field. Withdraw blood (non-heparinized) as needed, 20-30 ml for a 75 cm x 8 mm graft, larger volumes for larger grafts. It is important to leave some blood in Pan 1 after the graft is transferred to Pan 2. If, like a sponge, the graft has soaked up all the blood, it will not be possible to visually confirm that clotting has occurred in STEP 1. Use a new syringe for each withdrawal of blood.



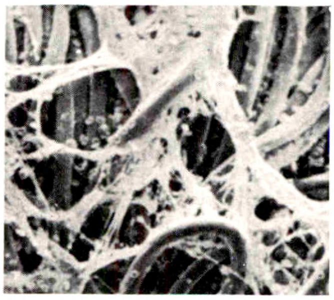
Wet graft in Pan 1 by injecting blood into lumen. After 2-3 minutes, remove the wet graft, stretch and place it in clean Pan 2.

The blood-soaked graft in Pan 2 awaits clotting of blood in Pan 1. During this time, fibrin is forming in the graft interstices—not in the lumen.





Blood now clotted. Thrombin present. Graft now ready for STEP 2.



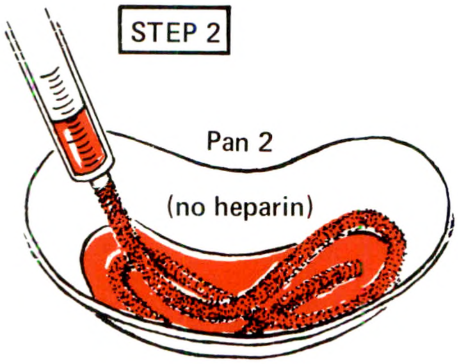
SEM of flow surface, x200

CAUTION:

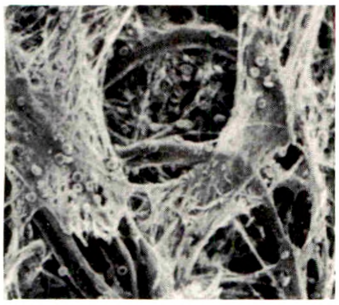
Should clotting fail to occur in Pan 1 after 7-8 minutes, repeat STEP 1. If clotting still fails to occur, add Thrombin, Topical. As thrombin will cause rapid clotting, quickly remove excess blood from graft with sponge to avoid intraluminal clotting.

FIG. 1. The Four-Step Preclotting Method: instructions on the sequential steps to be followed in preclotting a porous fabric prosthesis (USCI® Sauvage ™ Vascular Prosthesis) before giving systemic heparin. Scanning electron micrographs of graft flow surface illustrate appearances of the virgin graft and the same graft after each of the four steps.

STEP 2

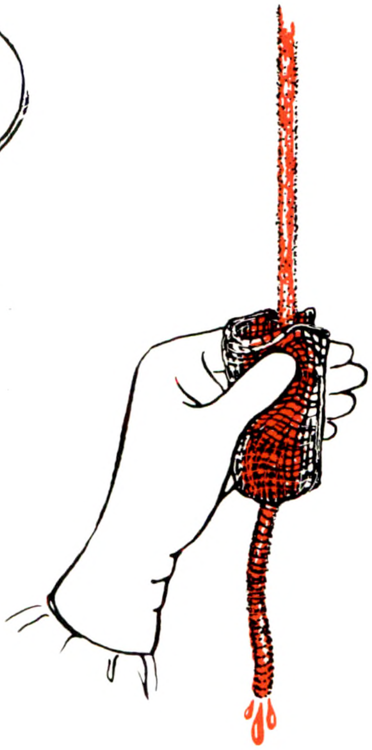


Inject another 20 ml of blood, but limit exposure to 20-30 seconds.

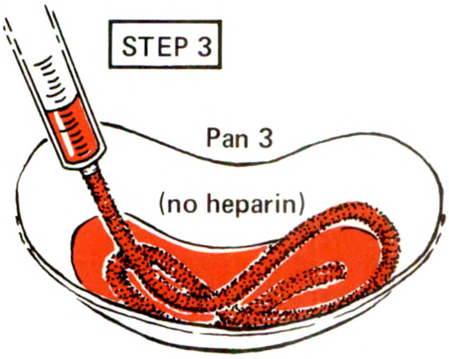


SEM of flow surface, x200

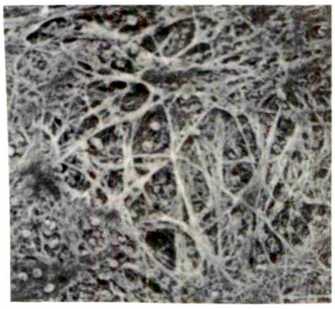
Strip excess blood from graft with sponge after blood injection in both STEPS 2 and 3.



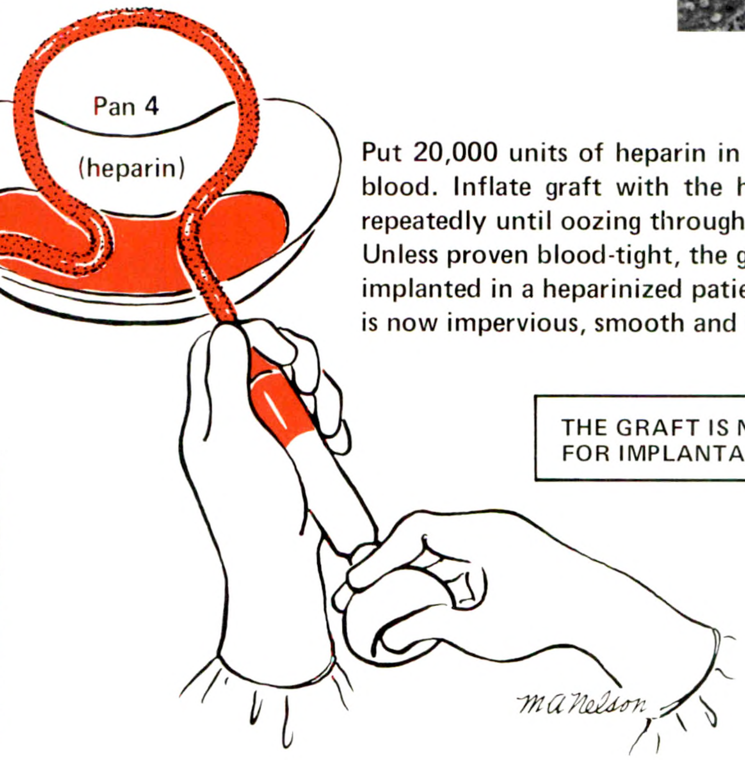
STEP 3



Inject another 20 ml of blood, but limit exposure to 10-15 seconds.



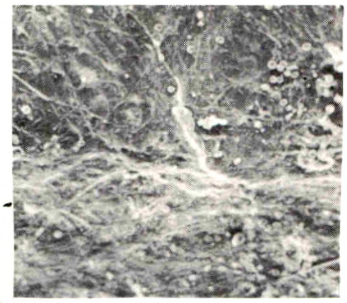
STEP 4



Put 20,000 units of heparin in Pan 4. Add 50 ml blood. Inflate graft with the heparinized blood repeatedly until oozing through graft wall has ceased. Unless proven blood-tight, the graft should not be implanted in a heparinized patient. The flow surface is now impervious, smooth and hypothrombogenic.

THE GRAFT IS NOW READY FOR IMPLANTATION

If there is concern that intraluminal fibrin septa may have formed in the graft, pull an inflated Fogarty embolectomy catheter through the graft.



SEM of flow surface, x200

The Four-step Preclotting Method

This four-step method systematically exploits the reaction between thrombin and fibrinogen to render a porous prosthesis* suitable for use in the fully-heparinized patient. To insure precise execution of the technique, it is designed to give the surgeon visual proof of proper completion of each step before proceeding. The four-step method entails repeated and controlled use of autologous thrombin to polymerize fibrinogen to fibrin, which seals the graft interstices. Finally, thrombin is neutralized by interaction with heparin. The four-step method and its salient points are emphasized and depicted in Figure 1.

The objective of Step 1 is to form thrombin. Therefore, it is absolutely essential for the surgeon to visually confirm that clotting has occurred in pan 1. Rarely, the patient's blood fails to clot and the graft cannot become impervious. In that circumstance, Step 1 is completed by adding a few drops of Thrombin, Topical (Parke-Davis, 1000 units/ml) to the blood. The use of topical thrombin will cause clotting to occur within 15–30 seconds, so the blood must be stripped quickly from the prosthesis to avoid intraluminal clotting. But with visible clot in pan 1, the graft is ready for Step 2.

The objective of Step 2, which utilizes thrombin generated in Step 1, is to form fibrin that can seal the graft interstices. Similarly, Step 3 utilizes thrombin from both Steps 1 and 2 with clotting proceeding at an accelerating rate because of increasing concentrations of thrombin.

The objectives of Step 4 are threefold: firstly, to seal tiny residual leaks; secondly, to demonstrate that the wall has become impervious; and thirdly, to neutralize all thrombin within the prosthesis. Any thrombin remaining in the graft wall after the need for fibrin formation has passed is unnecessary and undesirable. Indeed, graft thrombogenicity is not attributable to fibrin *per se*[21] but to persisting thrombin. Heparin, the only agent suitable for clinical neutralization of thrombin, interacts with thrombin in a stoichiometric manner.[24]† Three to four molecules of heparin are bound in each thrombin-anti-thrombin complex.[18] Thus, heparin is required in huge concentrations to inactivate the high concentration of thrombin formed during the preclotting of a porous fabric arterial prosthesis.

Experimental Data

Three series of experiments were performed in the carotid artery of the dog to assess the value of short-term heparin usage and to compare the values of the submersion and four-step preclotting methods with and without short-term heparinization. Healthy adult mongrel dogs weighing from 25 to 40 kg were anesthetized with pentobarbital sodium (Nembutal, Abbott, 100 units/mg). Access to both carotid arteries was gained by a midline incision. A 6 cm length of the mid-portion of a carotid artery was resected and the defect bridged with a 6 cm long, 4 mm diameter USCI Sauvage Filamentous Vascular Prosthesis. The anastomoses were performed in a continuous fashion using 7-0 Prolene placed either as an everting mattress or over-and-over suture. Seven days later the animals were given a high dose of pentobarbital and 10,000 units of heparin intravenously, and then sacrificed. The midsegment of the carotid artery bearing the graft was removed and opened to ascertain patency. The statistical significance of the patency rates within a series was determined by a chi-square distribution for independent samples.

The first series of experiments examined the effect of a full flow of high-dose (220 units/kg body weight) heparinized blood limited to the first 20 minutes after clamp release on the one week patency of grafts preclotted by the *in situ* method. In the second series, the one week patency rates of grafts preclotted by the four-step or submersion methods were compared in animals not receiving heparin. The third series compared the one week patency rates obtained with the four-step and submersion methods when combined with full flow of high-dose heparinized blood for the first 20 minutes after clamp release.

Series 1

Influence of an initial 20 minute graft exposure to full flow of high-dose heparinized blood after clamp release on the patency of bilateral carotid prostheses preclotted with whole blood *in situ*. The preclotting technique and protocol sequence for this series of experiments are illustrated in Figure 2.

After proximal and distal clamping of each carotid artery, a 6 cm length of vessel was resected. The proximal anastomosis of the first graft was performed and the distal end of this graft was occluded. The proximal clamp was intermittently released, allowing blood to pulse into the graft. The initial burst of blood was allowed to wet the graft for three minutes. Normal saline was then flushed into the graft lumen from the distal end. Subsequent exposures of the graft to blood

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* USCI Sauvage Filamentous Vascular Prosthesis.

† Thrombin inactivation is effected *in vivo* when anti-thrombin III (AT III) complexes with thrombin. Evidence indicates that when heparin binds to AT III via specific lysyl residues, a conformational change occurs in the AT III which markedly enhances the rate of formation of the thrombin-AT III complex and concomitant thrombin inactivation.[24,25]

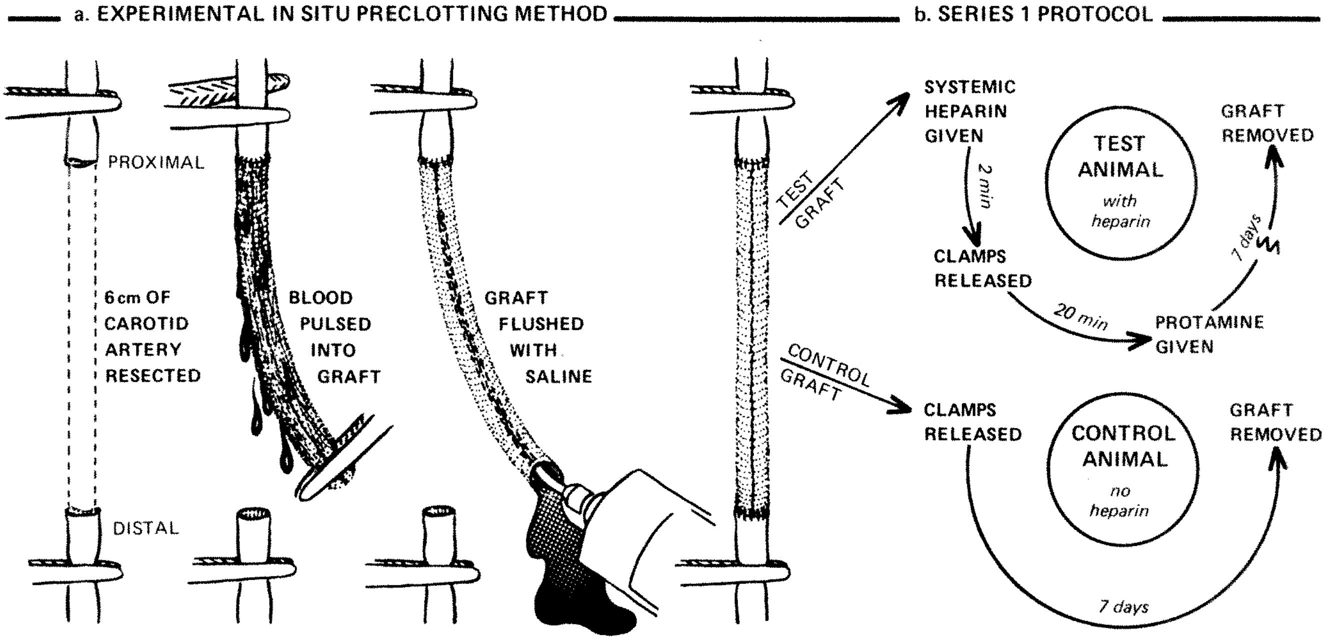

FIG. 2. Methodology of Experimental Series 1. (a) *In situ* preclotting of prosthesis implanted in the canine carotid artery. (b) Protocol sequence for test (with heparin) and control (without heparin) group of animals.

were limited to 15–30 seconds to minimize intraluminal clotting caused by rapidly accelerating flow surface thrombogenicity. This process was continued until the graft wall became impervious. The graft was flushed thoroughly with saline to remove intraluminal clot; then the distal anastomosis was performed. The second graft was implanted in the opposite carotid in an identical manner.

In test animals 220 units heparin/kg body weight (Upjohn, beef lung, 1,000 units/ml) were administered intravenously and allowed to circulate for two minutes before simultaneous release of clamps on both sides. Twenty minutes after clamp release 2.2 mg protamine sulfate/kg body weight (Lilly, 100 units/mg) were administered intravenously at a rate of 10 mg/min. Control animals received neither heparin nor protamine sulfate. In general, test and control studies were performed alternately.

Three identical sets of experiments, each involving 10 animals (sets A, B and C), were performed in this series. These studies were conducted intermittently over a 17 month period. Each animal received bilateral grafts. Hence, each set of ten animals comprised five receiving ten test grafts and five receiving ten control grafts.

The patency results from these three sets of experiments are shown in Table 1. In each of the three sets of studies, seven day patency was increased from 20%

TABLE 1. *Effect of Full Flow of High-Dose Heparinized Blood for the First 20 Minutes after Clamp Release on 7-Day Patency of Filamentous Dacron Prostheses Preclotted by an* in Situ *Method and Implanted in Canine Carotid Artery*

	Type of Experiment	Number of Grafts	Number of Dogs	Number Patent	Percentage Patent*
Set A	Systemic heparin flow for 20 minutes	10	5	7	70
	No systemic heparin	10	5	2	20
Set B	Systemic heparin flow for 20 minutes	10	5	7	70
	No systemic heparin	10	5	2	20
Set C	Systemic heparin flow for 20 minutes	10	5	7	70
	No systemic heparin	10	5	2	20
Totals	Systemic heparin flow for 20 minutes	30	15	21	70
	No systemic heparin	30	15	6	20

* These percentage patency differences are statistically significant ($p < 0.01$).

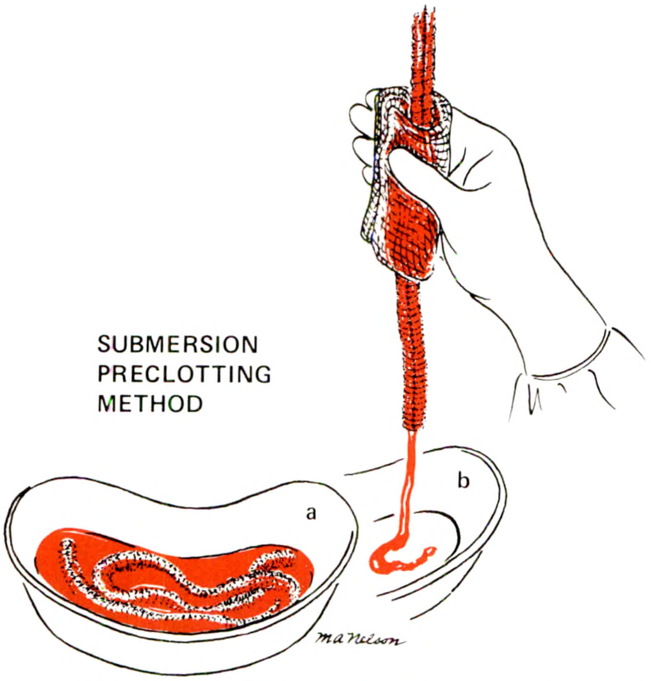

FIG. 3. The Submersion Preclotting Method: (a) Graft immersed in autologous whole blood until solid clotting occurs. (b) Graft stripped to remove clot.

(2 of 10) to 70% (7 of 10) by the high flow of heparinized blood for 20 minutes after clamp release. This improvement in patency is statistically significant ($p < 0.01$).

Series 2

Comparison of submersion and four-step preclotting methods when grafts were not exposed to heparinized blood after clamp release. The submersion preclotting method entailed graft immersion in autologous whole blood until solid clotting occurred (Fig. 3). The graft was stripped to remove clot. A 6 cm length was then used to bridge the carotid artery defect. Five grafts were implanted unilaterally using the right and left sides in alternate animals. The four-step preclotting method was employed for an additional five grafts which were implanted in an identical manner in alternate animals. Heparin was not given to any of these animals. The patency results are shown in Table 2. The patency of the submersion series was one of five (20%) while that of the four-step series was three of five (60%). In both series 1 and 2, graft patency was only 20% when the grafts were not exposed to heparinized blood after clamp release. In contrast, when the grafts were exposed to heparinized blood for 20 minutes after clamp release (series 1), 70% of the grafts were patent, and when it was employed only in the preclotting process (series 2) 60% were patent. While the data of series 1 are statistically significant ($p < 0.01$) the data of series 2 are not ($p > 0.10$). Although the results of series 2 lack significance (small numbers of experiments) they are compatible with the results of series 1 and 3.

Series 3

Comparison of submersion and four-step preclotting methods when grafts were exposed to full flow of high-dose heparinized blood for the first 20 minutes after clamp release.

The four-step preclotting method was employed to prepare ten grafts that were implanted in ten animals. After completion of anastomoses, 220 units heparin/kg body weight were administered intravenously and allowed to circulate for two minutes before clamp release. Twenty minutes after clamp release 2.2 mg protamine sulfate/kg body weight were administered intravenously at a rate of 10 mg/min. Ten grafts were preclotted by the submersion method and implanted in ten animals that received heparin and protamine sulfate in an identical manner. The patency results are shown in Table 3. All grafts (10 of 10) prepared by the four-step method plus systemic heparin for the first 20 minutes after clamp release remained patent. In contrast, only four of ten grafts prepared by the submersion method plus systemic heparin for the first 20 minutes after clamp release remained patent ($p < 0.05$). These results indicate that the attainment of flow surface hypothrombogenicity in preclotting is important and that exposure to short-term systemic heparin confers additional benefit.

TABLE 2. *Effect of Preclotting Method (Submersion vs Four-Step) on 7-Day Patency of Filamentous Dacron Prostheses Implanted in Canine Carotid Artery, When Grafts Not Exposed to Heparinized Blood*

Preclotting Method	Number of Grafts	Number of Dogs	Number Patent	Percentage Patent*
Submersion	5	5	1	20
Four-step	5	5	3	60

* These percentage patency differences are not statistically significant ($p > 0.10$).

TABLE 3. *Effect of Full Flow of High-Dose Heparinized Blood for the First 20 Minutes on 7-Day Patency of Filamentous Dacron Prostheses Preclotted by Submersion or Four-Step Method, and Implanted in Canine Carotid Artery*

Preclotting Method	Number of Grafts	Number of Dogs	Number Patent	Percentage Patent*
Submersion	10	10	4	40
Four-step	10	10	10	100

* These percentage patency differences are not statistically significant ($p < 0.05$).

Clinical Experience

The evolutionary development of the four-step preclotting method (Fig. 1) was complete by the end of 1973, and it has been used in standardized form since January, 1974. Reported herein are the results obtained in a consecutive series of 192 patients receiving USCI Sauvage Filamentous Vascular Prostheses preclotted by this method during the three year period January 1, 1974 through December 31, 1976 and followed through December 31, 1977. All grafts were implanted in fully-heparinized patients (200 units/kg body weight) with delay of protamine sulfate administration for 15–20 minutes after clamp release. This experience embodies five major categories of graft procedures: aortic bifurcation replacement after aneurysmectomy, aortofemoral bypass, femorofemoral crossover, axillary–femoral bypass and femoropopliteal bypass.

These 192 patients received a total of 300 graft limbs. For statistical purposes each limb of an aortic bifurcation graft, of an aorto-bilateral-femoral bypass and of a unilateral-axillary-bilateral-femoral bypass has been counted as a separate prosthesis. Mean implant time for the 300 grafts was 24.5 months. A total of 284 grafts remained patent while 16 closed. Patency for all implant sites was 94.7% with a range from 76.2% to 100%. Our four-year patency results obtained in the five main graft categories reported in life-table form (Figs. 4–8) are 100% patency for aortic bifurcation replacement, 100% for aortofemoral bypass, 93.5% for femorofemoral crossover, 81.8% for axillary-femoral bypass, and 66.1% for femoropopliteal bypass.

AORTIC BIFURCATION REPLACEMENT

patients	graft limbs	mean implant time	closures	patency
53	106	25.5 months	0	100%

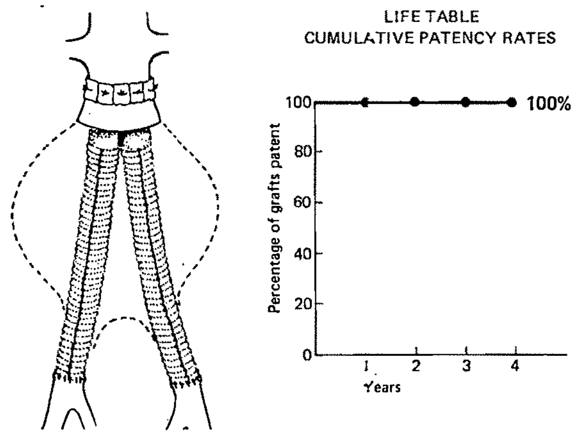

FIG. 4. A total of 106 aortic bifurcation limbs were implanted in 53 patients for an average of 25.5 months without any closures. These results compare favorably with published series.[11]

AORTOFEMORAL BYPASS

patients	graft limbs	mean implant time	closures	patency
42	84	25.6 months	0	100%

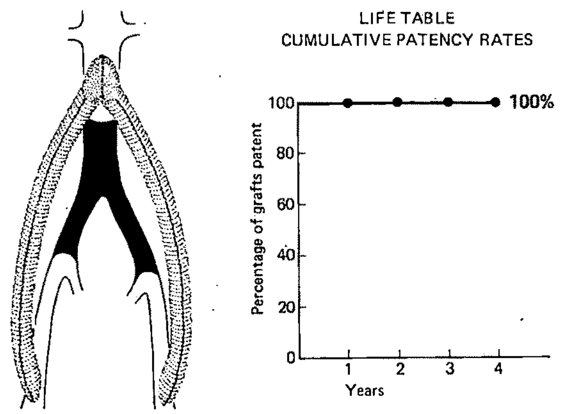

FIG. 5. A total of 84 aortofemoral graft limbs were implanted in 42 patients for an average of 25.6 months without any closures. These results compare favorably with published series.[11,16,17,19,22]

Clinical Perspective

The choice of preclotting technique in different circumstances for various procedures requires consideration of the advantages and disadvantages of each method. Table 4 summarizes the qualities of the four techniques available and presents our indications for their use.

Given a particular clinical situation, the surgeon must answer four questions. 1) What kind of graft should be employed? 2) If a porous graft is chosen, how should it be preclotted? 3) Should heparin be administered to the

FEMOROFEMORAL CROSSOVER BYPASS

patients	grafts	mean implant time	closures	patency
39	39	25.3 months	2	94.9%

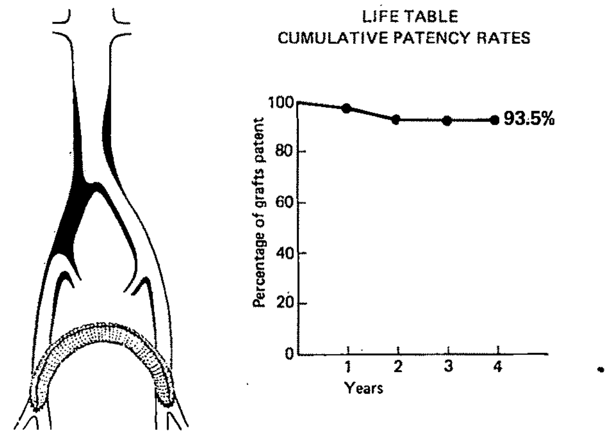

FIG. 6. A total of 39 femorofemoral crossover grafts were implanted in 39 patients for an average of 25.3 months with two closures. The patency rates compare favorably with published series.[1,12,23]

AXILLARY-FEMORAL BYPASS

patients	graft limbs	mean implant time	closures	patency
22	29	18.8 months	4	86.2%

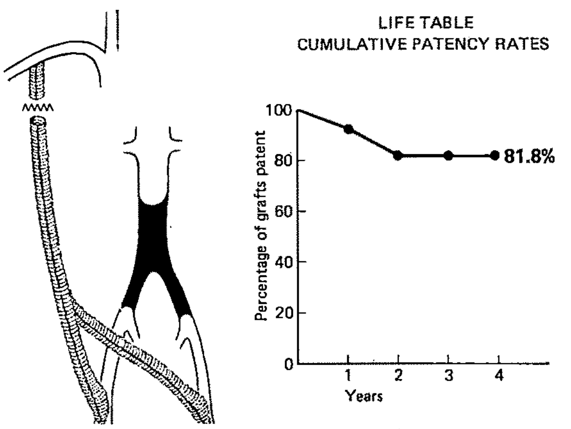

FIG 7. A total of 29 axillary-femoral graft limbs were implanted in 22 patients for an average of 18.8 months with four limb closures. The patency rates compare favorably with published series.[12,16,20]

patient? 4) If heparin is to be employed, should it be given systemically or only locally into the distal bed, and in what dosage?

We employ tightly woven prostheses for the ascending aorta and for dissecting aneurysms. Otherwise, the filamentous vascular prosthesis previously mentioned is used because of its better suturability and healing in comparison to woven prostheses. In addition, we believe that the preclotting and healing characteristics of this prosthesis are superior to other types of knitted prostheses. We employ the four-step preclotting technique in all clinical situations where this porous graft is used except in certain situations (*vide infra*) where large caliber, straight grafts are employed.

When the circulation is surgically interrupted we believe that heparin should be administered to protect the distal bed from stasis-induced thrombosis. This can be done intravenously or by downstream arterial injection. In general, we favor the use of heparin given intravenously in a dosage of 200 units/kg body weight. The use of systemic heparin has four advantages. Firstly, it renders the flow surface hypothrombogenic. Secondly, it protects the distal bed from thrombus formation. Thirdly, systemic heparin prevents blood in the operative field from clotting, including that which may seep into the graft. And finally, delayed neutralization of systemic heparin for 15–20 minutes after clamp release exposes the flow surface to a full flow of blood that cannot react by clotting. Procoagulants are washed away during these protected minutes. Additionally, the flow surface may be rendered passive by deposition of a very thin coat of protein, perhaps albumin.[2]

These experimental data indicate that the combination of the four-step preclotting method with an initial 20 minute exposure to a full flow of high-dose heparinized blood (220 units/kg) produces a better flow surface than that obtained with any of the other methods we have tried. The favorable clinical results we have obtained with this combination suggest that these experimental data are transferable to man.

However, in some clinical situations the use of large quantities of systemic heparin (200 units/kg) increases bleeding in the operative field to such an extent as to jeopardize the patient. Under these circumstances distal bed heparin injection (50 units/kg) should be employed.

In general, distal bed heparinization is indicated for fragile, aged patients, for those with ruptured aneurysms and for those requiring extensive dissection. When the abdominal aorta must be resected but the bifurcation can be saved, we employ a straight graft and protect the distal bed by injecting heparinized saline into the common iliacs. In such patients we usually do not use the four-step method; instead, we employ the *in situ* method illustrated in Figure 9. We initiate preclotting by wetting the graft with blood *before* any heparin is given. Then, after the upper anastomosis is performed, the preclotting process is completed by intermittently opening the proximal clamp to pulse short bursts of blood into the graft. Since the entire inner surface of such a large straight graft can be easily visualized, one can remove excess thrombus which may have formed. While the flow surface of a prosthesis prepared in this manner is highly thrombo-

FEMOROPOPLITEAL BYPASS

patients	grafts	mean implant time	closures	patency
36	42	23.0 months	10	76.2%

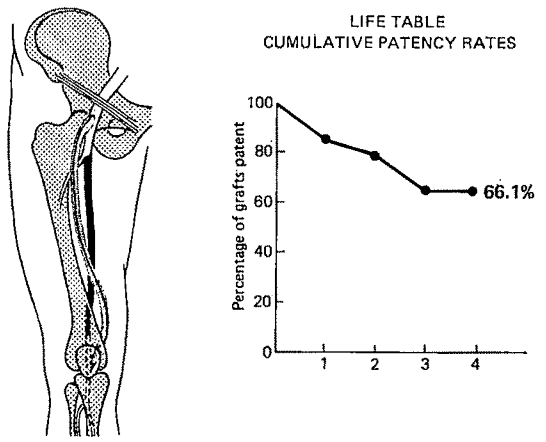

FIG. 8. A total of 42 femoropopliteal grafts were implanted in 36 patients for an average of 23.0 months with ten closures. The patency rates compare favorably with published series.[9,11,33]

TABLE 4. *Assessment of Preclotting Methods and Their Uses*

Preclotting Method	Feasible in Patient Given: A No Heparin	B Distal Bed Heparin	C Systemic Heparin	Preclotting Time	Blood Volume Required*	Graft Imperviousness	Flow Surface Smoothness	Thrombogenicity of Flow Surface	Applications and Indications for Use
1. Submersion	Yes	Yes	Unsafe	±10 min. for A and B; often no end point for C.	Variable; high if systemic heparin given	Variable	Variable	High	Limited value
2. *In situ*: Preliminary wetting with non-heparinized blood (see Fig. 9), followed by further exposure to blood after completion of proximal anastomosis	Yes	Yes	No	±3 min. for A and B; no end point for C.	Variable; may be very high if systemic heparin given	Variable	Variable	High	Straight, large caliber porous grafts when aortic bifurcation can be preserved and distal bed heparin employed. This technique (Fig. 9) is especially indicated in patients who (a) are frail or aged, (b) have a ruptured abdominal aneurysm, or (c) require extensive dissection
3. *In situ* variant: Exposure of dry graft to blood after completion of first anastomosis	Yes, but distal bed not protected	No	No	±10 min. for A; no end point for B and C.	May be very high; prohibitive if heparin given	Variable	Variable	High	Ill-advised
4. Four-step	Yes	Yes	Yes	15 min.	150 ml	Proven	Assured	Low	(a) all patients receiving porous grafts† in whom systemic heparin is used, (b) if distal bed heparin is employed the four-step method should be used if the flow surface cannot be visualized adequately as in long, small-caliber grafts†

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* For an aortic bifurcation graft. † Our studies have been confined to the USCI^{R} Sauvage$^{\text{TM}}$ Filamentous Vascular Prosthesis. The four-step preclotting method has not been evaluated with thin-walled, highly porous, non-filamentous fabric prostheses.

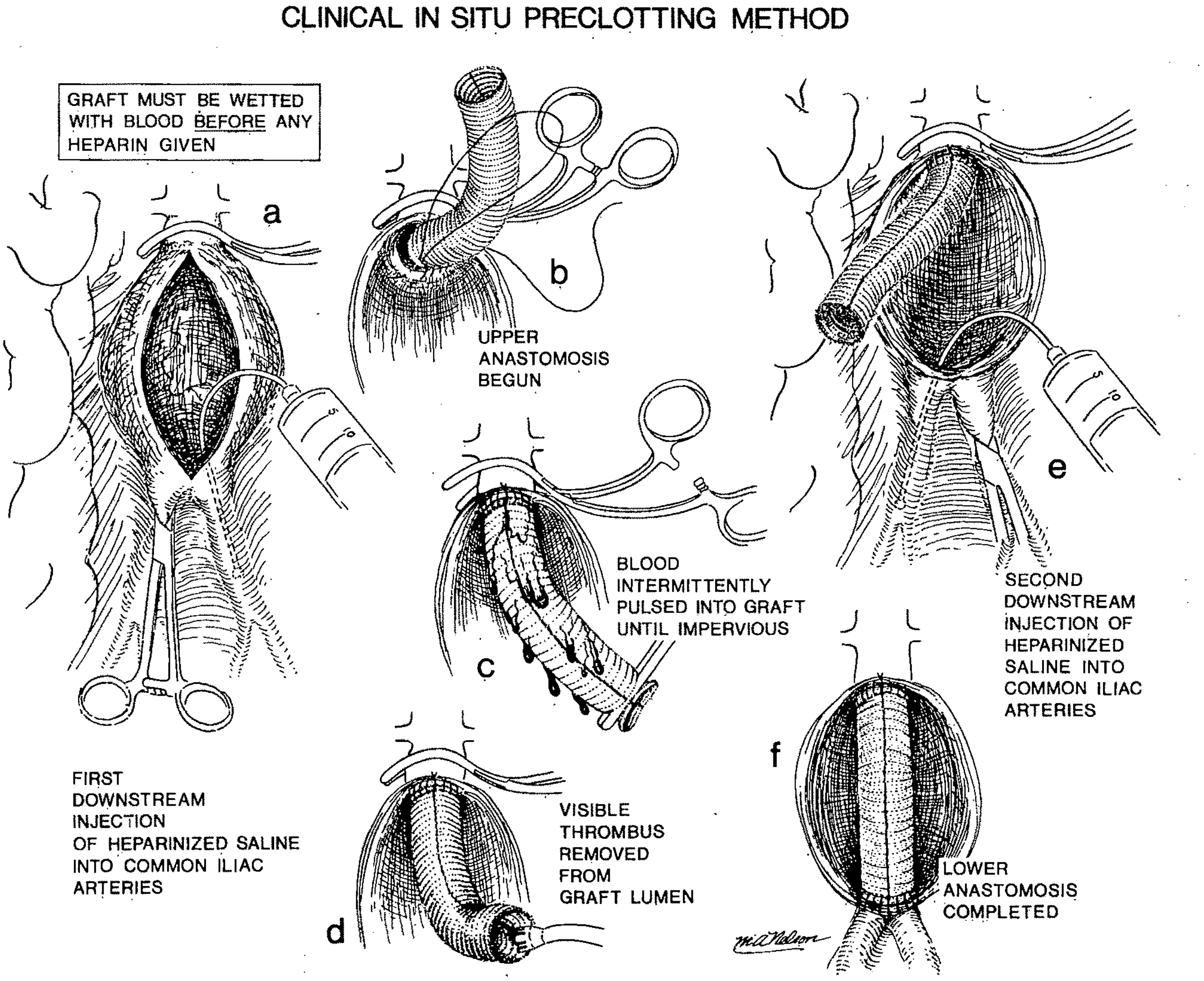
CLINICAL IN SITU PRECLOTTING METHOD
GRAFT MUST BE WETTED WITH BLOOD BEFORE ANY HEPARIN GIVEN
a
FIRST DOWNSTREAM INJECTION OF HEPARINIZED SALINE INTO COMMON ILIAC ARTERIES
b
UPPER ANASTOMOSIS BEGUN
c
BLOOD INTERMITTENTLY PULSED INTO GRAFT UNTIL IMPERVIOUS
d
VISIBLE THROMBUS REMOVED FROM GRAFT LUMEN
e
SECOND DOWNSTREAM INJECTION OF HEPARINIZED SALINE INTO COMMON ILIAC ARTERIES
f
LOWER ANASTOMOSIS COMPLETED

FIG. 9. Steps for *in situ* preclotting a straight graft when replacing abdominal aorta; distal bed protected by downstream injection of heparin into common iliacs. After the aneurysm is opened vertically, feasibility of preserving the bifurcation is assessed. If possible, it is saved and a straight graft is used. *Before* any heparin is given, the graft must be wetted with blood to initiate its preclotting. (a) After limited dissection, the infrarenal aorta and common iliac arteries are cross-clamped. Then the distal bed is heparinized by injecting 30 ml of heparinized saline into each common iliac (3,000 units heparin diluted in 100 ml normal saline). (b) After upper anastomosis is completed, graft is clamped distally (c) and the proximal clamp is released intermittently to pulse blood into the graft. Usually within two to three minutes the graft becomes blood-tight. As this occurs, the upper suture line can be checked and reinforced if needed. If the graft does not become blood-tight (an occurrence usually indicating failure to thoroughly wet the graft with blood before heparin was given, or that the graft was wetted with blood after the first distal bed heparin injection had been made) the inner surface of the graft should be bathed with a solution of Thrombin, Topical, and blood again pulsed into the graft to complete the *in situ* preclotting process. The graft, now blood-tight, is cut to proper length. (d) any visible thrombus within the graft lumen is extracted by suction under direct vision. (e) The distal bed is infused once again with heparinized saline. (f) The lower anastomosis is completed, after which the graft is covered by overlapping the residual aneurysm wall about it.

genic, this adverse characteristic is not significant in a large caliber aortic graft exposed to high flow, often above 1,000 ml/min.

If one fails to expose the graft to blood before injecting heparin into the distal bed, effective preclotting will be impossible without the addition of exogenous thrombin, for even the small amounts of heparin that then enter the systemic circulation from the distal bed will prevent clotting. Without active thrombin, the conversion of fibrinogen to fibrin cannot occur. But if clotting has already commenced in the graft (as in Step 1 of the four-step preclotting method), the high concentration of thrombin in the graft wall will not only neutralize the low concentration of heparin in the systemic blood, but will be more than adequate to form the polymer fibrin from fibrinogen and complete the preclotting process.

Caution is expressed against the use of the *in situ* preclotting method if the graft is long (aortofemoral) or of a caliber too small to permit adequate visualization of the entire flow surface. We recommend the four-step preclotting method in all such instances. This insures that there will be no build-up of clot on the inner wall and no fibrin septa crossing the lumen (Fig. 10).

The principle that an ideal flow surface should be impervious, smooth and hypothrombogenic cannot be challenged on a logical basis. We consider such a flow surface essential for patency of prostheses in small arteries, and have previously reported the successful use of porous filamentous fabric grafts in the right coronary of two patients.[29,32] We believe that the four-step preclotting method with delayed neutralization of systemic heparin gave these coronary grafts excellent flow surfaces which contributed substantially to their success. However, further experimental data and clinical documentation will be necessary before this or any other type of prosthesis can be recommended for selected use in coronary bypass, especially for the left coronary system where the flow may completely stop in early systole.

The submersion and *in situ* methods of preclotting have been used successfully in the aortoiliac area in thousands of patients since prosthetic grafts were introduced by Voorhees and Blakemore in 1952.[34] We believe that these imprecise methods have enjoyed success in this area because of the large caliber of the vessels and the high flow through them (400–600 ml/min). Furthermore, we believe that the undesirable flow surface characteristics of porous fabric prostheses preclotted by conventional techniques are sufficient reason to explain the early closure of such grafts employed for femorotibial bypass.[13] As the vessel caliber decreases, the flow surface criteria for continued patency become increasingly demanding.

The importance of precise preclotting in attaining a uniformly high success rate with porous fabric prostheses, even in the aortoiliac area, is borne out by the experimental and clinical data presented in this paper. We suggest that precise preclotting is of great value in medium caliber vessels, and is essential if prostheses of this type are to be used in small caliber vessels.

In recent years significant advances have been made in the development of prostheses that do not need preclotting. Two of these—a nontextile Teflon prosthesis (GORE-TEX®)* and a glutaraldehyde-processed, externally-supported umbilical vein homograft (Meadox Biograft®)†—have been used clinically with considerable success for femorotibial bypass.[3,5–8] Currently it is thought that porous fabric prostheses cannot be used successfully for femorotibial bypass. However, the case against the use of such prostheses in this area is incomplete because only crimped prostheses have been employed and they have been preclotted by the imprecise submersion or *in situ* methods.

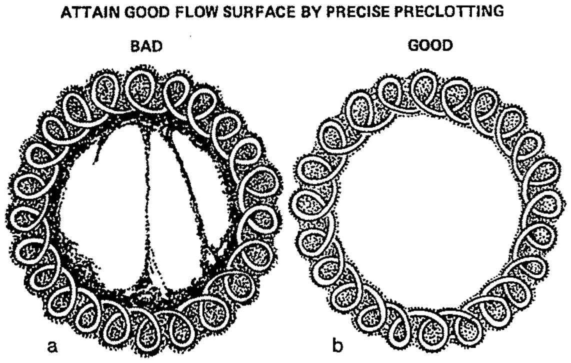

FIG. 10. Diagrammatic cross-section of preclotted grafts to show bad flow surface (a) and good flow surface (b). These results depend upon the preclotting technique employed. The bad flow surface is apt to occur if long or small-caliber grafts are preclotted by either the submersion or *in situ* methods. The figure illustrates the thick and irregular lining of thrombus with cross-channel fibrin septa which may form. The good flow surface should be routinely obtained for any length or caliber of graft if the four-step preclotting method shown in Figure 1 is performed accurately. The proper application of this method assures that the inner lining will be very thin and the flow surface impervious, smooth and hypothrombogenic.

Preliminary experimental data from this laboratory (to be published) show that a 4 mm diameter, *noncrimped*, porous filamentous Dacron® prosthesis prepared by the four-step preclotting method and an initial 20 minute exposure to full flow of heparinized blood has a substantially lower thrombotic threshold velocity (velocity at which thrombosis begins) in the canine carotid artery than the Biograft prosthesis. In contrast, the Gore-Tex prosthesis has a thrombotic threshold velocity comparable to that of the properly preclotted, noncrimped, porous, filamentous Dacron prosthesis. Additional unpublished findings show the seven day patency rate of the fabric prosthesis in the canine carotid artery has been higher than that of either the Gore-Tex or Biograft prostheses.

Summary

A new preclotting method is presented which reliably produces an impervious, smooth and hypothrombogenic flow surface in porous filamentous fabric prostheses. This method enables these prostheses to be used safely in fully-heparinized patients. It involves four steps and is moderately more complex than the submersion or *in situ* methods in common use. The flow surface of a prosthesis preclotted in this manner is further enhanced by exposure to full flow of high-dose heparinized blood for 15–20 minutes after clamp release. The advantages of this approach in terms of patency have been fully substantiated by the results of controlled experimental studies and four years of clinical experience. We believe that the use of this preclotting method is of value even with large caliber porous filamentous fabric prostheses and is essential for those of small caliber.

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* GORE-TEX®, manufactured by W. L. Gore & Associates, Flagstaff, AZ.

† Biograft®, manufactured by Meadox Medicals, Oakland, NJ.

Acknowledgments

The authors gratefully acknowledge the outstanding work of Barbara Blakemore, Dennis Johnson, Betty Larson, Michael Lischko and Dorothy Mungin, whose diligent efforts made possible the results reported herein. Thanks are also due to Lou Taylor for his valuable help in the preparation of the manuscript.

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Fasting and Postprandial Serum Gastrin Levels in Infants with Congenital Hypertrophic Pyloric Stenosis

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Recently attempts have been made to demonstrate the possible role of hypergastrinemia in the production of congenital hypertrophic pyloric stenosis in infants. Eleven infants with congenital hypertrophic pyloric stenosis, ranging in age from three to 11 weeks, were evaluated for fasting and postprandial serum gastrin levels. Two to ten weeks following successful pyloromyotomy, a similar evaluation was undertaken to demonstrate the possible role of elevated serum gastrin levels in the etiology of congenital hypertrophic pyloric stenosis. The average fasting and postprandial serum gastrin levels in infants with congenital hypertrophic pyloric stenosis did not differ significantly from levels noted in control infants. Similarly, no statistically significant difference was noted between the pre- and postoperative levels of serum gastrin in the affected infants. Several experimental studies have been reported within the past few years describing the production of hypertrophic pyloric stenosis in the offspring of dogs injected with pentagastrin during pregnancy. The results of our study minimize the direct importance of serum gastrin in the production of congenital hypertrophic pyloric stenosis. The role of the hormone secretin in the etiology of this condition is hypothesized.

SINCE THE ORIGINAL ANATOMIC description of congenital hypertrophic pyloric stenosis by Hezekiah Beardsley, in 1788,[1] this disorder has been recognized as the most common congenital anomaly of the gastrointestinal tract requiring surgical correction. Despite a striking familial tendency, the etiology of congenital hypertrophic pyloric stenosis remains obscure. Although various hypotheses have been suggested, recent interest has focused on the gastrointestinal hormone, Gastrin. The possibility that elevated serum Gastrin levels contribute to the development of congenital hypertrophic pyloric stenosis was first suggested in 1970, by Dodge,[2] when he managed to produce in puppies pyloric "tumors" closely resembling infantile hypertrophic pyloric stenosis by injecting the dams with Pentagastrin during pregnancy. The present study was designed to evaluate fasting levels of serum Gastrin in human infants with congenital hypertrophic pyloric stenosis and the response in the serum levels of this hormone following ingestion of a high protein meal.

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Materials and Methods

Eleven infants with congenital hypertrophic pyloric stenosis were evaluated, ranging in age from three to 11 weeks at the time of initial diagnosis. Eight infants were male and three were female. Body weights ranged from 2.4 to 4.5 kg at the time of initial evaluation. Following diagnosis, all infants underwent nasogastric decompression for 18–24 hours. Serum Gastrin levels were determined on 1.5 ml of venous blood in the fasting state and at 15, 30, and 45 minutes following a standard meal. The standard meal consisted of a protein concentrate (Sustagen) providing 1.7 g protein per kg body weight. An identical evaluation was performed two to ten weeks following surgical pyloromyotomy. Five infants of comparable age and weight were employed as controls and underwent similar evaluation of fasting and postprandial serum Gastrin levels. All blood samples were analyzed for Gastrin by the radioimmunoassay described by McGuigan.[7] Levels were determined in triplicate and the average of these was used as the value of serum Gastrin for each specimen. Informed consent was obtained from the parents of each infant evaluated on this protocol.

Results

The average fasting serum Gastrin levels in infants with congenital hypertrophic pyloric stenosis did not differ significantly from levels noted in the control infants (128 pg/ml vs 125 pg/ml). Both of these values are somewhat lower than the fasting values noted in normal 72-hour-old infants in our institution (average 195 pg/ml),[6] but these differences are not statistically significant ($p > 0.05$) (Fig. 1). Infants with congenital

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Submitted for publication: March 10, 1978.

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hypertrophic pyloric stenosis as well as control infants manifested a normal postprandial elevation in serum Gastrin levels after ingestion of the high protein meal. Although infants in the control group appeared to have a somewhat higher postprandial elevation in serum Gastrin levels up to 45 minutes following the protein meal, these values did not differ statistically from those observed in the group with congenital hypertrophic pyloric stenosis ($p > 0.05$) (Fig. 2). Using a Mann-Whitney U-test to compare the serum Gastrin responses to a protein meal in the control and affected infants, no statistical differences were noted at any time interval. In the infants with congenital hypertrophic pyloric stenosis, there was no statistical correlation between the maximum serum Gastrin level achieved following protein ingestion and the age or weight of the patient at the time of observation. In the postoperative studies in patients with congenital hypertrophic pyloric stenosis, a similar rise in serum Gastrin concentration was noted in response to protein ingestion, but no significant differences were observed from preoperative studies ($p > 0.05$) (Fig. 2).

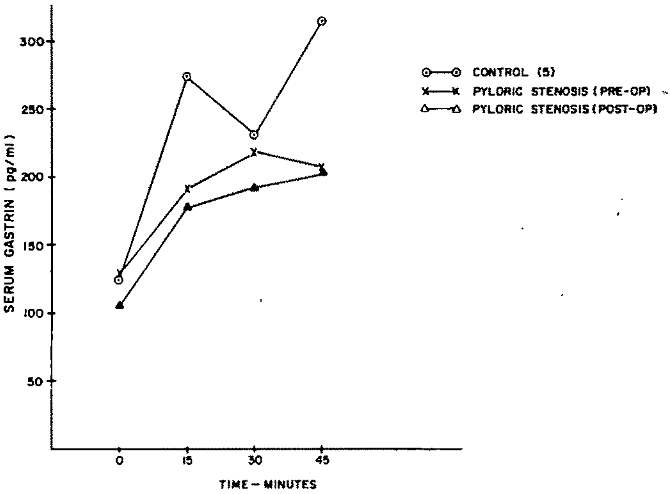

FIG. 2. Average pre- and postprandial serum Gastrin levels in control infants and infants with congenital hypertrophic pyloric stenosis before and after pyloromyotomy. Normal postprandial elevations are noted in each group in response to protein feeding. No significant differences were noted between the responses of these groups of infants.

Discussion

In spite of the frequency of this disorder, the etiology of congenital hypertrophic pyloric stenosis remains obscure. Interest in the role of Gastrin in the production of hypertrophic pyloric stenosis was initiated by experiments reported by Dodge, in 1970.[2] Injecting the hormone Pentagastrin into pregnant dams in the final trimester of gestation and into the newborn puppies, Dodge was able to produce a lesion that was grossly and histologically similar to congenital hypertrophic pyloric stenosis in 28% of these puppies. This work was confirmed by two subsequent studies reported by Karim and Dodge, in 1974 and 1975.[3,6] These authors postulated that Pentagastrin caused chronic pylorospasm, ultimately leading to pyloric muscular hypertrophy. Evaluating this hypothesis, Rogers, in 1975,[8] studied 15 infants with congenital hypertrophic pyloric stenosis. After a three-hour fast, these infants had a mean serum Gastrin concentration of 163 pg/ml as compared to a control group of normal infants with a fasting level of 193 pg/ml. These differences, however, were not statistically significant. Five days following pyloromyotomy, the infants with hypertrophic pyloric stenosis had a fasting serum Gastrin value of 205 pg/ml, a value which was not statistically greater than their preoperative levels. A similar study was reported by Spitz, in 1976,[9] evaluating serum Gastrin in 18 infants with congenital hypertrophic pyloric stenosis after a 24 hour period of nasogastric decompression. These infants had a mean preoperative serum Gastrin value of 170.5 pg/ml compared to the control infant value of 99.6 pg/ml. The fasting serum Gastrin level of these infants was found to rise to 204 pg/ml four days following pyloromyotomy. Unlike the earlier studies of Rogers, these authors noted these differences to be statistically significant, and speculated that the differences noted between their group of infants and that reported by Rogers were caused by differences in the time period of nasogastric decompression prior to obtaining blood samples for the Gastrin levels.

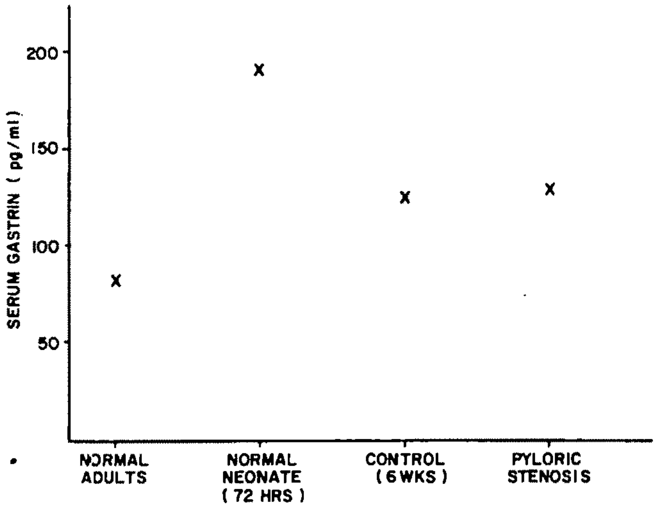

FIG. 1. Average fasting serum Gastrin levels of normal adults and neonates compared with fasting serum Gastrin levels in a group of control infants and those with congenital hypertrophic pyloric stenosis.

These conflicting studies have raised questions as to the significance of basal hypergastrinemia in the pro-

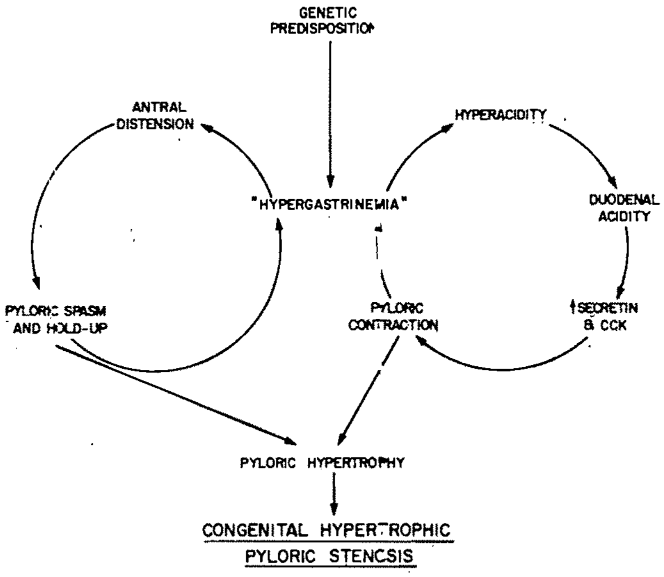

FIG. 3. Proposed mechanism for the production of congenital hypertrophic pyloric stenosis. In face of a genetic predisposition, either exogenously administered Gastrin or normal neonatal hyperacidity cause an increase in duodenal acidity with release of the duodenal hormone Secretin. As suggested in the cycle on the right, the eventual outcome could be pyloric spasm and hypertrophy. The left cycle represents events previously suggested as playing a possible role in the mechanism for production of congenital hypertrophic pyloric stenosis.

duction of congenital hypertrophic pyloric stenosis in human infants. Both of these clinical studies have left unanswered the possibility of excess postprandial hypergastrinemia as a possible etiological factor in this disorder, even if fasting serum Gastrin levels were normal. To evaluate this possibility, our study was performed with 11 infants with congenital hypertrophic pyloric stenosis. As with the infants in Rogers' study, our children with congenital hypertrophic pyloric stenosis demonstrated no significant basal hypergastrinemia as compared to a control group of normal infants. Following ingestion of a standard meal, high in protein, these infants demonstrated appropriate elevations of serum Gastrin levels which were not significantly higher than those noted in the control population. These data indicate that exaggerated postprandial hypergastrinemia is not noted in human infants with congenital hypertrophic pyloric stenosis. In recent experimental studies, Gastrin has been shown to increase gastric antral motility in humans, but paradoxically has been found to decrease gastric emptying time.[4] Fisher[5] has demonstrated, with both *in vitro* and *in vivo* experiments, that Gastrin does not cause pyloric contraction in the human, but actually appears to cause some degree of pyloric relaxation. These authors further documented that the gastrointestinal hormone Secretin appears to have a significant contractile effect on the human pylorus. We feel that this finding may provide an explanation for the ability of Dodge and Karim to produce hypertrophic pyloric stenosis in puppies injected with Pentagastrin. Fifteen per cent of these puppies were noted to have duodenal ulcers, an indirect evidence of gastric hypersecretion in these animals. The increase in gastric acid output resulting from the Pentagastrin injections might be expected to increase the extent of duodenal acidification resulting in secondary release of Secretin from the proximal duodenum and this excessive release of Secretin may produce chronic pyloric spasm, leading eventually to hypertrophy of the pylorus in these animals. Perhaps in the presence of a genetic predisposition for pyloric spasm, the normal neonatal hyperacidity in the human infant leads to an elevation in duodenal acidity with increase in Secretin release (Fig. 3). The resulting pyloric spasm may contribute to the eventual development of congenital hypertrophic pyloric stenosis.

Conclusions

Consideration of our data appears to minimize the direct importance of serum Gastrin in the production of congenital hypertrophic pyloric stenosis, as suggested by previous experimental and clinical studies. The present clinical study appears to rule out the possibility of exaggerated postprandial hypergastrinemia in this condition. Further studies in infants with congenital hypertrophic pyloric stenosis will be necessary to elucidate the importance of the gastrointestinal hormone Secretin in the etiology of this disorder.

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Hyperbilirubinemia in Inflammatory Pancreatic Disease:

Natural History and Management

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Of 868 patients admitted with pancreatitis between 1971 and 1976, coexisting hyperbilirubinemia was noted in 125 (14%). The patient population was primarily composed of alcoholics (84%) with chronic pancreatic disease (75% Marsielles Class II or higher) which was of moderate severity (77% fewer than three prognostic signs). The hyperbilirubinemia in these 125 patients was due to extrahepatic obstruction in 22%, hepatocelluar disease in 31%, and was idiopathic in 47%. Transient hyperbilirubinemia (< 10 days duration) occurred most commonly in the idiopathic group. Transitory periductular pancreatic edema may account for the elevated bilirubin in some of these cases. Liver biopsy should be done whenever hyperbilirubinemia persists longer than ten days in patients with pancreatitis. If hepatocellular disease is not found, transhepatic or endoscopic retrograde cholangiography are indicated. If common bile duct obstruction is demonstrated, a brief trial of medical therapy is in order. Persistent conservative treatment, however, exposes the patient to the risk of cholangitis and biliary cirrhosis. In 13 of the 125 cases (10%), persistent extrahepatic obstruction proved to be due to compression of the common bile duct by inflammatory pancreatic tissue. In these circumstances, choledochoduodenostomy is recommended as the procedure of choice. In patients requiring biliary decompression, concommitant procedures upon the pancreas are occasionally indicated.

For more than 80 years it has been known that obstructive jaundice may result from inflammatory pancreatic disease.[10] Although a number of studies have appeared in the recent literature[4,7,11,12] fewer than 100 documented cases of jaundice due to benign pancreatic disease have been reported. Since each of the previous communications has been restricted to describing a small number of surgical cases, the general approach to the management of patients with hyperbilirubinemia and pancreatitis continues to be problematic.

How frequently do pancreatitis and hyperbilirubinemia coexist? When does the demonstration of an elevated bilirubin in patients with pancreatitis indicate the necessity for surgery? What are the risks in untreated cases? What is the preferred surgical technique?

The purposes of the present study are twofold: 1) to provide both incidence and natural history information in order to more clearly define therapeutic roles in this condition and, 2) to describe our experiences in the management of thirteen cases requiring surgical correction.

Patient Data

Records of all patients with a diagnosis of pancreatitis admitted to Grady Memorial Hospital between 1971 and 1976 were reviewed. In 868 patients, the clinical diagnosis of pancreatitis was substantiated by characteristic upper abdominal pain and constitutional symptoms, abdominal tenderness, and elevated serum and/or urine amylase. Patients not meeting these criteria or those subsequently proved not to have pancreatitis were excluded. In recent years, the diagnosis of pancreatitis has frequently been confirmed by demonstrating an elevated amylase clearance.

Of the 868 patients with pancreatitis, 125 (14%) also exhibited a total serum bilirubin greater than 1.5 mg/100 ml. It is with these 125 patients with pancreatitis and hyperbilirubinemia that the present study is concerned.

The *type* of pancreatitis present in these 125 patients is considered in Table 1. That this study is weighted toward a more chronic form of pancreatitis is evidenced by noting that three patients out of four were Marsielles Class II or higher. Chronic alcoholism was predominant in 105 (84%) of these 125 patients. Cholelithiasis was the primary feature in 11 (9%), and in five cases (4%), both alcoholism and cholelithiasis were present.

The *degree* or severity of the pancreatitis exhibited by these patients is shown in Tables 2 and 3. Ninety-six patients (78%) exhibited fewer than three of those signs

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Submitted for publication: February 18, 1978.

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Table 1. *Type of Pancreatitis in the Study Group**

Class	Type		
I	Acute	27	
II	Acute relapsing	51	92
III	Chronic relapsing	39	
IV	Chronic	2	
		125	

* Marsielles classification.

Table 3. *Severity of the Associated Pancreatitis*

Number of Prognostic Signs	Number of Patients	Hospital Deaths	Mortality Rate
0	28	0	3/96 (3%)
1	39	2	
2	28	1	
3	13	3	6/29 (21%)
4	10	0	
5	1	1	
6	5	2	
7 or >	—	—	
	125	9	9/125 (7%)

known to be of prognostic significance.[9] Of note is that the mortality rate was seven times higher when three or more of the prognostic signs were present. In addition to the nine in-hospital deaths, an additional 16 patients subsequently expired from various causes making the total known mortality rate 25/125 (20%). As an additional reflection on the severity of the underlying pancreatitis in these patients, 44 of these 125 patients (35%) required at least one readmission during the study period for recurrent pancreatitis.

Significant features of the past medical history included a history of upper gastrointestinal bleeding in 41, alcoholic ketoacidosis in 22, profound weight loss in 22, and insulin dependent diabetes mellitus in eight cases.

The physical findings in this group of patients primarily reflected the acute nature of the episode; abdominal tenderness was noted in 114, and body temperature was elevated above 38.5° in 72 patients. Liver percussion exceeded 12 cm in 33 cases.

Three laboratory values were of specific interest (Table 4). Although total bilirubin was abnormally elevated in *each* of the 125 patients, the highest value recorded was less than 6 mg% in 108 cases (86%). Amylase was elevated in 98 of the 115 cases in which it was measured.

The causes of the hyperbilirubinemia in the 125 patients with coexisting pancreatitis are listed in Table 5. Fifty-eight patients exhibited a mild elevation of bilirubin returning to normal within ten days. Work-up of these patients was not extensive and they are accordingly classified as idiopathic. Sixteen patients were found to have biliary lithiasis. In none of these patients, however, including six with choledocholithiasis, could any stricture of the common bile duct be demonstrated at surgery. Of interest is the observation that only 28 of these 125 patients (22%) harbored surgically correctable hyperbilirubinemia.

Table 2. *Prognostic Signs**

Admission		First 48 Hours	
Prognostic Sign	No. Patients	Prognostic Sign	No. Patients
LDH > 350 IU	52	CA < 8 mg%	26
Glucose > 200 mg%	35	Hct decrease > 10 units	11
SGOT > 250 sfu	26	Pa_{O_2} < 60 torr.	9
Age > 55 years	17	BUN increase > 5 mg%	8
WBC > 16,000 mm^3	15	Base deficit > 4 meg/L	7
		Fluid sequestration > 6 L	6

* After Ranson, et al.[9]

Of the 125 patients with pancreatitis and hyperbilirubinemia, only 13 (10%) underwent operative correction for compression of the common bile duct by pancreatic tissue (Table 6). That inflammatory pancreatic disease uncommonly results in significant common bile duct obstruction is further emphasized by the observation that of the 868 patients in this study admitted for pancreatitis, only 1.4% required surgery for hyperbilirubinemia due solely to pancreatitis.

Sufficient clinical suspicion of common bile duct obstruction to warrant investigation of bile duct morphology arose whenever *persistent* hyperbilirubinemia was demonstrated. In 58 of 92 cases in whom it was possible to determine the duration of hyperbilirubinemia, serum bilirubin returned to normal within 10 days or less. All 13 of the patients eventually shown to have common bile duct obstruction requiring surgery were in the group of 34 patients with hyperbilirubinemia persisting longer than ten days. Patients requiring surgery also exhibited significantly higher average values for total bilirubin 12.6 ± 1.9 mg% and for alkaline phosphatase 986 ± 160 mu ($p < .01$).

Discussion

Since the terminal portion of the common bile duct is encased by pancreatic tissue in 60–80% of patients,[5]

Table 4. *Serum Values of Interest*

	Normal	Avg. + SEM	Range
Amylase	<200 Somogyi U.	687 ± 119	39–5400
Total bilirubin	<1 mg%	3.9 ± 0.4	1.5–28
Alkaline phosphatase*	5–13 King-Armstrong U.	30.9 ± 5.5	7.9–124
	35–100 milliunits	196.0 ± 17.0	38–900

* Reported in KA during 1971–72; milliunits in 1973–1976.

TABLE 5. *Causes of Hyperbilirubinemia in 125 Patients with Pancreatitis*

Medical causes		
Alcoholic hepatitis	19	
Cirrhosis	8	
Drug induced	6	
Hepatitis (+Australia Ag)	4	
Hemolysis	2	
	39	(31%)
Obstruction of bile duct		
Benign pancreatic disease	13	
Cholecystolithiasis	10	
Choledocholithiasis	6	
	29	(22%)
Idiopathic	58	(47%)
	125	(100%)

it is not surprising the hyperbilirubinemia occurs in patients with benign pancreatic disease. Rather, it seems remarkable that jaundice does *not* accompany pancreatitis even more frequently.

Initial recognition that chronic pancreatitis could cause compression of the common duct has been credited to Riedel[10] who reported a single case in 1896, although Mayo-Robson reported a series of 10 cases in 1904, one of which had been operated upon in 1892.[6] Since that time, a number of smaller anecdotal reports have appeared concerning this condition.[2,3,7,8,11–13] Presently, however, there are fewer than 100 documented cases in the literature.

Despite the infrequent reporting of such cases, it is likely the hyperbilirubinemia secondary to pancreatitis is more common than generally appreciated. Frieden examined 300 autopsy records of patients with acute pancreatitis and found 25% with coexisting jaundice. Only 16%, however, were due to pancreatic encroachment on the common duct.[3] By being limited to autopsy material and correspondingly severe disease, these incidence data may not reflect the entire disease spectrum of pancreatitis. Weinstein and his coworkers similarly estimated the incidence of jaundice in pancreatitis to be 15–25%.[13] They further proposed that periductal pancreatic edema could account for the *transient* obstructive jaundice observed in some patients with acute pancreatitis.

In the present study, we found that while hyperbilirubinemia occurred in 125 of 868 patients with pancreatitis (14%), hyperbilirubinemia could be solely attributed to pancreatitis or its complications in only 10%. (13/125). What proportion of the 58 "idiopathic" patients with transient hyperbilirubinemia were in fact due to pancreatic causes was not determined in this study. It is likely that hyperbilirubinemia in some of these patients was due to compression of the intrapancreatic portion of the common duct by edema arising from the adjacent pancreatitis.

Accordingly, these data suggest that a rational plan of management for hyperbilirubinemia coexistent with pancreatitis would consist of initial supportive treatment and observation. Should hyperbilirubinemia persist longer than ten days, liver biopsy should be considered. In approximately 25% of our cases, the liver biopsy was diagnostic of primary hepatocellular disease. If the liver biopsy shows cholestasis, visualization of the biliary duct system by endoscopy or thin needle cholangiography would seem indicated. Radiographic demonstration of a dilated common bile duct taken in conjunction with an elevated alkaline phosphatase and hyperbilirubinemia is definitive proof of significant obstruction.

A brief trial of conservative therapy is probably warranted in patients with persisting obstruction. However, if both the elevated alkaline phosphatase and total bilirubin do not promptly return to normal, continued medical treatment may expose the patient to the risk of cholangitis. Cholangitis occurred in two of the thirteen patients undergoing surgery in this study (cases 2 and 11), and has been reported by others.[4,12] Furthermore, long standing obstruction even of a relatively mild degree, apparently disposes toward biliary cirrhosis.[12] In this regard, an isolated persistent elevation of alkaline phosphatase may be the earliest expression of significant duct obstruction, and, when found, should initiate investigation.

Surgical treatment is quite successful in relieving persistent biliary obstruction. Although a variety of techniques for biliary drainage can be used, choledochoduodenostomy and Roux-en-y cholecystojejunostomy have provided the best long term results.[11,12] In our opinion, choledochoduodenostomy offers three advantages over Roux-en-y cholecystosjejunotomy or Roux-en-y choledochojejunostomy: 1) bile is not diverted from the duodenum 2) future pancreatic surgery is not compromised, and 3) stricture of this anastomosis is decidedly uncommon. We believe that whenever choledochoduodenostomy is done, cholecystectomy should be added in order to prevent accumulation of food debris refluxed into the common duct.

Regardless of which technique is chosen, it is imperative to construct a large biliary–intestinal stoma in order to prevent postoperative stricture and subsequent episodes of cholangitis.

In addition to biliary drainage, concommitant procedures upon the pancreas may occasionally be indicated. In particular, pseudocysts should be drained at the same time that biliary obstruction is relieved. If the pseudocyst is in the head, cystoduodenostomy may be chosen. It is important to obtain an operative cholangiogram after drainage of pseudocysts in the head of the pancreas, since biliary obstruction may be due to causes other than the pseudocyst itself (cases

TABLE 6. *Patients Requiring Surgical Relief of Common Bile Duct Obstruction Caused by Inflammatory Pancreatic Disease*

	Age	Sex	Duration of Hyperbilirubinemia	Findings at Surgery	Operation	Results
1	49	M	2 Months	Mass in head of pancreas	Roux-y cholecystojejunostomy Biopsy–chronic pancreatitis	Occasional episodes of pancreatitis in 2 yr. follow-up
2	39	F	3 Weeks	Inflammatory mass in head Suppurative cholangitis	Exploration and T-Tube Drainage of common duct	No recurrence in 18 months
3	49	F	2 Weeks	Pseudocyst in head of pancreas	Cystoduodenostomy	Expired 14 days later in renal failure. Autopsy showed obstruction of common duct by chronic pancreatitis
4	42	M	9 Weeks	Firm mass in head of pancreas	Roux-y cholecystojejunostomy	Occasional episodes of pancreatitis in 3 yr. follow-up
5	39	M	2 Weeks	Pseudocyst in head of pancreas	Cystoduodenostomy Biopsy–chronic pancreatitis	Asymptomatic 1 yr. follow-up
6	54	M	2 Weeks	Pseudocyst in head Ampullary stenosis	Cystoduodenostomy Sphincteroplasty Biopsy–chronic pancreatitis	Recent discharge
7	49	F	4 Months	Firm mass in head of pancreas	Roux-y cholecystojejunostomy	Expired 5 yrs. later in alcoholic ketoacidosis. Autopsy showed fibrotic obstruction of common duct.
8	42	M	4 Weeks	Firm mass in head of pancreas	Choledochoduodenostomy Biopsy–chronic pancreatitis Incidental cholecystectomy	Recent discharge
9	36	M	5 Weeks	Firm mass in head of pancreas	Choleochoduodenostomy	Asymptomatic for 6 months
10	47	F	6 Weeks	Large mass in head of pancreas	Cholecystojejunostomy with enteroenterostomy	No recurrence in 5 yrs.
11	32	F	2 Months	Mass in head of pancreas Ascending cholangitis	Roux-y choledochojejunostomy Cholecystectomy	Asymptomatic for 1 yr.
12	31	F	6 Weeks	Mass in head of pancreas	Choledochoduodenostomy Biopsy–chronic pancreatitis Incidental cholecystectomy	Occasional episode of pancreatitis during 3 yr. follow-up
13	41	M	3 Weeks	Large mass in head of pancreas Duodenal obstruction	Whipple procedure Biopsy–chronic pancreatitis	Asymptomatic for 6 months

3 and 6). One of our patients (case 13) underwent pancreaticoduodenectomy when persistent obstructions of the common bile duct, the pancreatic duct, and the duodenum were demonstrated. It should be kept in mind that biliary drainage alone does not offer any respite from the ongoing fibrotic process in the pancreas, and that continued symptoms may require corrective pancreatic surgery at some future time.

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William Halsted and Theodor Kocher:

"An Exquisite Friendship"

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William Halsted and Theodor Kocher were friends on both a professional and personal level. They greatly admired each other's surgical skills and judgement, and Halsted was a frequent visitor to Kocher in Switzerland. This is of interest in that both men have been described as introverted personalities with very few intimate acquaintances. An analysis of their personal correspondence, which has not been previously published, clearly demonstrates this unique relationship between the two reknowned surgeons.

IN 1927 WILLIAN MACCALLUM, Professor of Pathology at the Johns Hopkins Hospital and biographer of William Halsted, wrote to Albert Kocher son of the Nobel laureate surgeon Theodor Kocher:[6] ". . . Dr. Halsted was I know a very intimate friend of your father . . . and the relationship which existed between them has always seemed to me a very exquisite friendship and full of interest . . ."

It was an exquisite friendship indeed, on both a professional and personal level. Although Halsted's educational philosophies had been most influenced by the intense scientific scholasticism of mid-19th century Germany,[24] it was the Swiss born Kocher who he admired more than any other modern surgeon, and with whom he was most closely bound by ties of friendship, frequent association and highest professional regard. Both Warfield M. Firor and William F. Rienhoff, Jr., who served as assistant residents under Halsted, corroborate this fact, and emphasized that Halsted continually referred to Kocher as the greatest technical surgeon of his time, and one who the House Staff would do well to emulate.[1,23]

Albert Kocher (1872–1941) wrote of their association:[7]

> ". . . My father liked Halsted very much, and I must say there were very few surgeons with whom he was as intimate. Halsted would come to Berne for some little time, say two to three weeks, and every day attended the clinical lectures and operations of my father, who took him to all his visits to the patients, and made him examine the interesting cases. Afterwards, Halsted would lunch regularly in our family house, and there all the cases of the morning were discussed . . .
>
> Many times the two men met in Berlin for the German Surgical Congress. They both stayed at the Hotel Adlon, and were together the whole time. It was my father, as a member of the committee of the German Surgical Society, who proposed Halsted as an honorary Fellow.
>
> The two men were a bit equal in their character. Both not tall nor massive as some surgeons are, but very fine, delicate, distinguished looking. Their exterior was very modest, and yet very noble, very grand, always kind to everyone, more especially to the patients of inferior classes and yet very energetic and severe when important things were at hand . . ."

Harvey Cushing (1869–1939) was one of the few men who studied with both Halsted and Kocher. He has commented:[2]

> ". . . I couple their names together for they had much in common. They were engaged in similar problems; they were friends and correspondents; they were equally fastidious in their operative craftsmanship and at the same time, by precept and example, exerted a profound influence as investigators on the scientific aspects of their art. They represented European and American surgery of their day at its very best . . ."

This paper will examine the relationship of these two reknowned surgeons through an analysis of their personal correspondence. These letters have not been

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Supported by the Robert Wood Johnson Foundation (Dr. Rutkow is a Robert Wood Johnson Clinical Scholar).

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previously published, and they provide a vivid insight into the "working" friendship of the two famous scientists.

Halsted (1852–1922) (Fig. 1) was 11 years younger than Kocher (1841–1917). This age differential was further accentuated by a difference in their age of attainment of professorial rank. Kocher (Fig. 2) was appointed Professor in the University of Bern surgical clinic at the early age of 31. This was five years before Halsted was to receive his M.D. degree, and 20 years prior to his being named Surgeon-in-Chief and Professor of Surgery at the Johns Hopkins Hospital.[21]

Although Halsted had made numerous trips to Europe during the early phase of his professional life, it was not until 1899 that he actually met Kocher. He had spent several days in Bern in the summer of that year, and the beginnings of the friendship took place. It is easy to understand how Halsted was drawn so close to Kocher. Kocher's habit of "tediously studying surgical problems from their anatomical and pathological aspect before beginning to apply surgical methods to their cure was so much Halsted's own way of approach that there could not fail to spring up a real intellectual sympathy between them".[21] Kocher has been quoted as saying:[2] ". . . surgeons who take unnecessary risks and operate by the clock are exciting from the onlookers' standpoint but they are not necessarily those in whose hands you would by preference choose to place yourself . . ."

Halsted, in a similar way, was an exacting and extremely slow operator. There were no signs of anything dexterous or showy, but instead a close observance to detail and a tireless concentration of attention upon every minute aspect of a procedure. During Halsted's first visit to Bern he closely observed all the technical methods used in Kocher's clinic, and especially all the modifications of instruments which had been introduced there. He took care to buy at once such instruments, as he thought valuable for his own use, on his return to Baltimore.

There was little in the way of further personal contact between the two men and their families until May, 1907 when Albert Kocher visited America and took part in a symposium sponsored by the American Medical Association. At this particular meeting the results of the study of Halsted's operative material from exophthalmic goiter were presented,* emphasizing the observation of the presence of masses of lymphoid tissue in such thyroids and the complication of surgical tetany from thyroid surgery.[3] Kocher reported a correlated discovery of an increase in the number of lymphoid cells in the blood of a person with exophthalmic goiter.

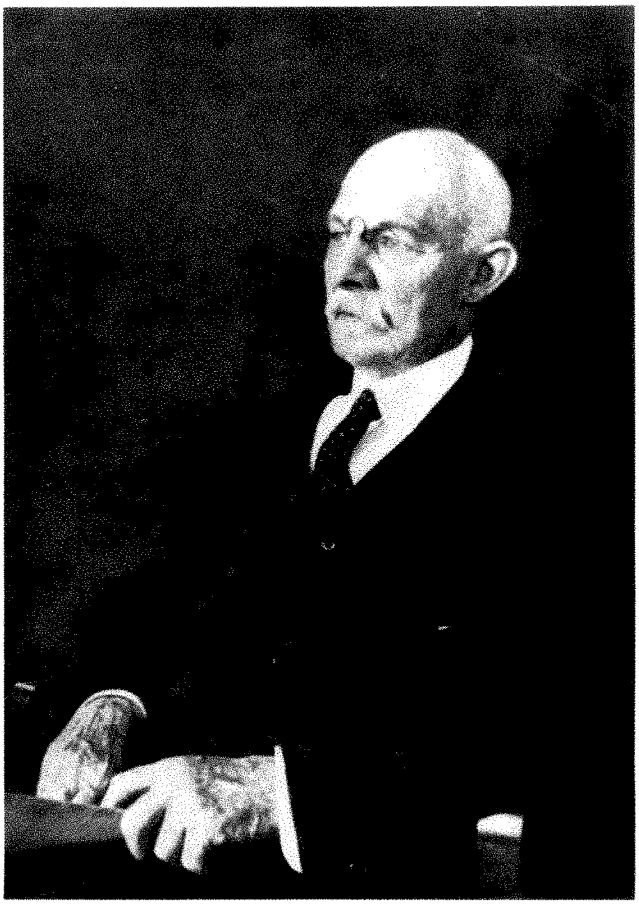

FIG. 1. William Halsted in 1922.

In the summer of that year, Halsted made a trip to Europe which included a stay with the Kochers. In a letter to Richard Follis, his former Chief Resident, he described the visit:[19]

> "Dear Follis- Tuesday-July 11, 1907
>
> I am just leaving Berne for Paris. Have had a most enjoyable sojourn here and am actually driven away by the excessive hospitality of the Kochers. Have dined only twice alone since you left having taken all other dinners and all luncheons with the Kochers. Once when I positively declined an invitation to dinner Professor Kocher himself came to the hotel with a written invitation from Mrs. K. and naturally I succumbed. You can picture to yourself my embarrassment . . ."
>
> W.S.H.

In the summer of 1911 Halsted sailed on a Hamburg-American Line ship and landed at Hamburg. He spent

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* Prior to the opening of the Johns Hopkins Hospital in 1889, Halsted had spent considerable time in William Welch's laboratory studying the physiology of the thyroid gland. His interest, on this subject, however, had waned until 1904 when he began to again perform numerous experimental surgical procedures on the parathyroid, thyroid and thymus glands.

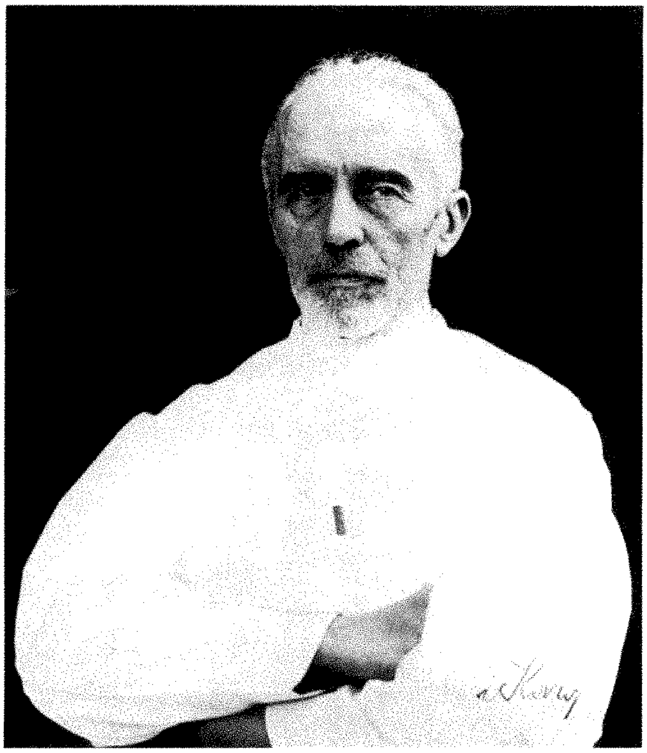

FIG. 2. Theodor Kocher in 1911.

several days with Kummell at his clinic, and even attended some horse races sitting several rows behind Kaiser Wilhelm. From Hamburg he went to Berlin where he observed Bier's surgical clinic. After ten days he then traveled to Switzerland and spent time with Kocher. Although Halsted had always felt ill at ease about performing surgical procedures while in Europe, he was asked to and actually did operate on a patient with an abdominal aortic aneurysm during the stay in Bern. He described the operation in a letter to his sister, Mrs. John T. Terry, Jr. (Fig. 3):[20]

"Darling Bertie London July 26, 10 P.M.

> . . . You are such a dear sister that I am about to send you a photograph taken at Professor Kocher's clinic at Berne at the close of an operation which I was performing upon an old woman for the cure of an aneurism of the aorta. Professor Kocher had kept the patient in his clinic for six weeks awaiting my arrival. He happened to know of my interest in these cases and of experimental work which I have been conducting for about six years with view to curing just such a case as this proved to be. The operation up to the day of my departure from Berne seemed likely to prove even more successful than I had dared hope for this patient. The operation consisted in the partial occlusion of the abdominal aorta by an aluminum band applied by means of an instrument which I have devised. During the greater part of the operation I was on the opposite side of the table, but at the last moment had to transfer myself to the patient's left side. Five or six cameras, my assistants told me, were fired off during the first part of the operation, but not a single picture was successful. Only the final

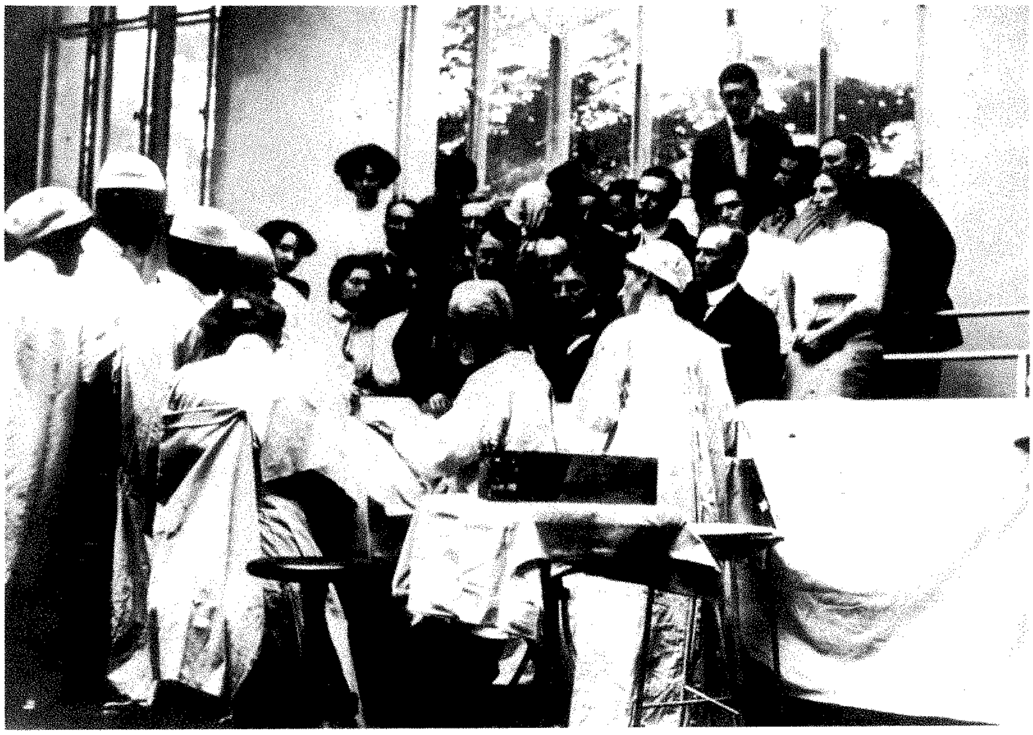

FIG. 3. Halsted and Kocher operating on a patient with an abdominal aortic aneurysm (1911).

one, taken by the operating room orderly, *surreptitiously*, was worth preserving. You will observe that a nurse is dodging so as to bring my bald head (snow capped) into view. Professor Kocher is seated on the opposite side of the table. The heads of my three assistants, Follis, Sowers and Fisher, form a triangle, the centre of which is filled in by the nurse at Professor Kocher's back. The remainder of the audience is composed of doctors from foreign parts, visitors of the clinic who were invited to see the operation. Fortunately, little is to be seen of me except the noble brow. I am not very vain on the subject of my features as you may well understand . . ."

Albert Kocher wrote to Halsted upon the latter's return to America:[8]

"Dear Professor Halsted,

I wanted long ago to write to you and tell you how glad we were to have you here for some days. The assistants had the photograph in the operating room enlarged and sent it to my father on his 70th birthday, so we have the recollection of your visit. I want to tell you about your patient with the aneurysm. You had still watched the reduction of the size which lasted, the pulsation was much less, and the patient had lost her pain entirely. There was no trouble in her legs, and her heart behaved quite well. In the middle of August we were about to let her go home, as she is living quite near the hospital, but she began to be a little feverish in the evening. After a few days nothing could be made out as to the source of the fever, but she complained of pain on the top of the aneurysm and it was slightly sensitive to touch. There was no change in blood pressure or the quality of the pulse . . . One morning 6 weeks after the operation she collapsed in a few minutes with symptoms of burst aneurysm. In the autopsy 2½ liters of blood were in the abdomen but the aneurysm showed no perforation, on the contrary its size was much reduced, ¾ of its lumen was filled with solid thrombi adherent to the wall. Passage was quite free through it. Above the sac a spurious aneurysm had formed, the metal band having worked slowly through the wall . . . We think if the edges of the band could be made smoother such a thing would not happen. There was no sign of infection or abscess. We hope Dr. Finney will send us his wire for aneurysm of the aorta, and we are keeping two cases for it . . . Hoping you are quite well, believe me yours very sincerely."

Dr. Albert Kocher

The treatment of arterial aneurysms by metal banding had been investigated at some length by Halsted. He had written extensively on the subject, and had included the patient with the fatal rupture of the false aneurysm in his report to the American Surgical Association in May, 1913. His poor experience with the metal band and its inevitable cutting through the attentuated aortic wall led to the alternative use of bands of fresh aorta and fascia lata for subsequent aneurysm treatment.[4]

In 1912 Halsted was again in Bern for the Kocher jubilee. The following year he visited Breslau, Leipzig and Würzburg and spent a week in Switzerland. It was after his return home that there began an extraordinary exchange of letters concerning thyroid surgery and its attendant complications (Fig. 4):[9]

"My Dear Sir 15. 10. 13

I have heard with great interest your report on some 30 cases of Basedow operation,* especially as I see that you succeed in cutting away the posterior part of both lobes and can without any danger ligate 4 arteries. Have you as a rule done this excision of both lobes at one time and ligated 3 or 4 arteries at the same time? and always without any bad symptoms? If so, how can you arrest bleeding in cutting through the goiter tissue? Do you put a 'Massenligature' on the part you leave behind? Have you followed your cases long enough to be sure that with the ligature of 4 arteries or the resection of both lobes you never get a myxoedema?

I have seen cases where myxoedema resulted as a consequence of too much cutting off of goiter . . . Have you found the method of de Quervain more useful for the performance of ligature of the inferior thyroid artery than the usual way of intracapsular ligation? . . .

I am sorry to say that I have to tell the committee of the International Surgical Congress that I shall not come to New York next April, my wife being always too anxious to let me travel on a steamer for America. I am sure that it will be a great success; you have so wonderful things to show.

Believe me yours most sincerely"

Theodor Kocher

Two weeks later Halsted answered Kocher's letter in detail:[10]

"Dear Professor Kocher:- October 28, 1913

It gratifies me very much to receive your letter this morning and to be reminded that you take such a friendly interest in my work. I have ligated the thyroid arteries in the most serious cases—cases in

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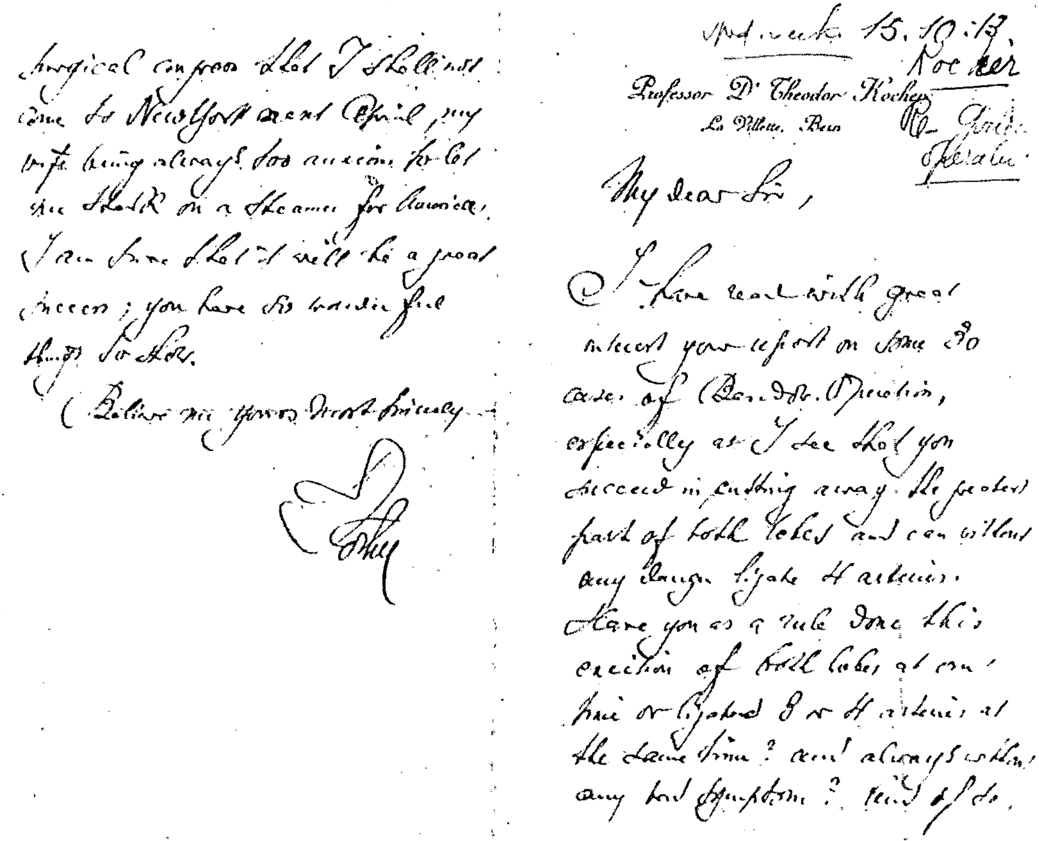
* Basedow is a synonym for Grave's disease.



surgical congress that I shall not come to New York next April, my wife being always too anxious to let me start on a steamer for America. I am sure that it will be a great success; you have so wonderful things to show.

Believe me yours most friendly

[illegible] 15. 10. 13.

Kocher

Re Goiter operation

Professor Dr Theodor Kocher
La Villette, Bern

My dear Sir,

I have read with great interest your report on some 90 cases of Basedow's disease, especially as I see that you succeed in cutting away the greater part of both lobes and can without any danger ligate 4 arteries. Have you as a rule done this excision of both lobes at one time or ligated 3 or 4 arteries at the same time? and always without any bad symptom? [illegible]

FIG. 4. A letter from Kocher to Halsted (October 15, 1913).

which I feared to perform lobectomy. In only three cases was it deemed necessary to tie all four of the arteries before venturing to excise a lobe, and in these cases both lobes had to be excised because only slight improvement followed the excision of the first lobe. In none of these cases did symptoms of parathyroid deprivation supervene. In four other cases, however, of double lobectomy, mild tetany developed, but for a few days only . . .

As to the ligation of the inferior thyroid artery, I have never employed the intra-capsular method. I cut directly down on the common carotid artery where the tendon of the omohyoid muscle should cross it. The carotid is retracted outwards, the thyroid gland inwards, the thyroid artery is exposed by the use of two long, fine dissectors through a space which usually hardly admits one finger . . . I tie the inferior in preference to the superior arteries . . . Before incising the thyroid tissue all the blood vessels—large and small—supplying the lobe are clamped but not cut, and in this way bleeding is avoided. The clamps are plunged a little way into the thyroid tissue and made to seize the vessels at some distance from the beginnings of their course on the gland. Thus the circulation of the parathyroid and the recurrent laryngeal nerves are not endangered . . . After excision of the lobe all the vessels are occluded by transfixion ligatures, some continuous some interrupted . . . I am sorry to hear that you cannot attend our Congress in the spring, but still cherish fondly the hope that you and Mrs. Kocher may soon come to America. The voyage is so comfortable and simple . . . it is very rapid and quiet on the large new vessels such as the Lusitania . . .

Will you give my kindest messages to Mrs. Kocher, to Dr. Albert, and to all the members of your family, and believe me,

Very sincerely yours,"

W. S. Halsted

There were obvious differences which the two surgeons used in their operative approach to goiter. Kocher condemned the method of mass ligation of the arteries because of the intimate relation of the inferior thyroid artery to the recurrent nerve. Halsted practiced "ultraligation" of the blood vessels. That is, by tying the thyroid arteries beyond the point at which the parathyroid arteries were given off, the preservation of a vascular source to the parathyroid gland was maintained. Kocher never approved of the procedure to remove the greater part of both lobes. He performed, in all except exceptional cases, a one-sided lobectomy. Halsted, however, frequently removed part of each lobe especially in cases of colloid goiter and milder forms of Grave's disease. He was of the conviction that partial resection should be done in place of total lobectomy in order to protect both the parathyroids and recurrent nerve, and to preserve a slice of thyroid in case an operation might have to be performed on the opposite lobe. Halsted also felt that Kocher had never learned how to effectively deal with a thickened isthmus.[5]

In 1914 Halsted traveled twice to Europe, once in April for the forty third Congress of the German Surgical Association in Berlin, where he spent most of the time with Kocher, and again, later in the summer, when he found the arrangements for his return very difficult because of the outbreak of World War I.

Halsted has written of the Spring trip:[11]

> ". . . In the Spring of 1914 I spent a week with Kocher in Berlin. We were constantly together except at breakfast, being invited to the same houses and when not dining out, taking the evening meal quietly together at the Hotel Adlon, and occasionally going to the theatre afterwards . . . I found myself almost always in hearty sympathy with his methods and views. There was no other surgeon with whom I could discuss surgical matters so satisfactorily and in such a sustained fashion . . ."

On his return to the United States Halsted wrote to Kocher:[12]

> "Dear Prof. Kocher:- May 2, 1914
>
> . . . I am still feeling the exhilaration of the week in Berlin, and uppermost in my mind at all times is the marvelous kindness shown me by you and your son . . . I earnestly hope that I may be able to attend the Congress next year, and do something to atone for the long and inappropriate paper which I read last month . . .* I am sending Mrs. Kocher a folder description of the new ship Columbus of the North German Lloyd Line, hoping that I may be able to persuade her to come with you to America.
>
> Sincerely and gratefully yours,"
>
> W. S. Halsted

Unfortunately Halsted never attended another Congress of the German Surgical Society, and Kocher was not to travel to the United States. They were never to meet again although their correspondence continued:[13]

> "Dear Prof. Halsted, July 24, 1916
>
> . . . . I am all right again, but will still go for some weeks to a holiday in the mountains. Mrs. Kocher and Albert will accompany me, as soon as they are both weary from all the work which must be finished . . . I have to give a report on complications of goiter in the beginning of next year at the meeting of the Swiss Surgical Society (Roux is the president after I have left the presidential chair). I wonder if you have changed your practice of excision of goiter. Do you always perform *double* resection in Basedow's and hyperplastic goiter in leaving back only a thin sheath of glandular tissue at the back part? Always avoiding to put the ligature on the main vessels and taking the branches near the glandular home? Where did you first publish the double resection? It was probably before Mikulicz had recommended resection against excision or enucleation. Prof de Quervain has strongly advocated this double method for other than Basedow's goiter, but he begins with ligation of all 4 arteries except the posterior branch of 1 inferior. I am afraid that after a while he will see symptoms of myxoedema arise in the nonBasedow goiter . . .
>
> With my kindest regards to Mrs. Halsted from us all.
>
> Sincerely yours,"
>
> Theodor Kocher

Kocher had contracted a severe case of pneumonia in the winter of 1916, but even this did not seem to decrease his enthusiasm for work. At the age of 75 he was as active as ever engaging in both clinical and experimental studies, in addition to his duties as a teacher of medical students.[22,25] Halsted's last letter to Kocher was written eight months before the latter's death:[14]

> "Dear Professor Kocher: November 28, 1916
>
> I am writing merely to send you and Mrs. Kocher and all members of your family my best wishes for the New Year, and to let you know that I am ever mindful of your many kindnesses to me in Berne and Berlin. There seems to be no prospect of peace and I am beginning to fear that I may never again attend a meeting of the Deutsche Gesellschaft für Chirurgie or see my German friends.
>
> I have just been reading a paper by Prof. de Quervain . . . on goitre. He pays me a fine compliment, for which I am grateful to him but he entirely miscomprehends what I mean by "ultraligation" of the vessels to the thyroid gland which I make in performing lobectomy.
>
> He has the impression that I mean by ultraligation the tying of the inferior thyroid artery at some distance from its parathyroid branch . . . The fact is that I have never tied the inferior artery in lobectomy operations. Instead of doing so I clamp all the branches of distribution to the lobe at some distance

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* The paper which Halsted refers to is titled "Der Partielle Verschluss Grosser Arterien", and was presented on April 16, 1914.

from the hilus of the gland and resect the gland (leaving a slice posteriorly to protect the parathyroids and the recurrent nerve) before ligating the vessels . . .
I hope that you have recovered your normal, I might say abnormal vigor, and I hope that Mrs. Kocher and your sons are quite well.
I am with highest regard and affection,"

Yours very truly,

W. S. Halsted

On July 23, 1917 Kocher complained of a severe headache, nausea, vomiting and diarrhea. He died four days later. Halsted was greatly grieved by the loss. Letters of sympathy were sent, and he maintained his correspondence with the Kocher family:[15]

"My Dear Dr. Albert; February 18, 1918

Can you send me a good biographical sketch of your father . . . I hope he may have left an autobiography. Please tell me something of his last illness and of his state of health from the time of his recovery from pneumonia until the end. I trust that my letters of sympathy to you and Mrs. Kocher were not lost on the way. Is Mrs. Kocher quite well? and how are you, and what are your plans for the future. I was sorry to learn that you were not appointed successor to your father in the Chair of Surgery at Berne . . .

Sincerely yours,"

W. S. Halsted

Albert Kocher answered four months later:[16]

"My dear Professor Halsted. June 10, 1918

. . . we received your letters of sympathy and also answered them, but nowadays so many letters go astray. Of course we are still suffering very much from the great loss, it is such a change in everything . . . My father took a rest for 5 months after his pneumonia as he had several relapses . . . I proposed at that time, in October 1916, that he should give up a little of his great work and put more on my shoulders, but he was too active a man and too interested in his work, to do so and we had the pleasure of seeing him as fresh as ever during the whole winter and summer session. Ten days before his death he said to one of his colleagues, that he had never been too well. About a fortnight before that he was suddenly taken with sickness and vomiting and diarrhea and stayed in bed 2 days and afterwards complained of some headache. Four days before his death he finished his lectures and operated that same day but had a headache, so that he examined himself and his water and found albuminuria. The next day he got up, and there was a very little albumin, but in the afternoon severe headaches and vomiting came on . . . and in the evening of the same day, lost consciousness in a uremic coma. He did not wake up before his death, 36 hours later. It was so very sudden that he did not realize at all his coming end and I must say now, how good it was for him to leave all his work, as a man in the full thought, being able to do his full work till the end. He would have been very unhappy, had he been obliged to live as an invalid . . .
There was a good deal of jealousy against my father here, and that is the real cause of my not being appointed his successor. Of course de Quervain is a good surgeon and very capable. I am trying to work with him now, but of course there is such a difference between him and the great man, my father was . . .

Yours always sincerely,"

Albert Kocher

By the summer of 1918 war had engulfed all of Europe, and the supremacy of German surgery was soon to end. Although the Swiss populace had not been involved in the armed struggle, they were directly affected by the savagery which surrounded them:[17]

"My dear Professor Halsted Aug 11th, 1918

. . . we are getting short of food in Switzerland, and are very glad that the United States can do as much for us as they can. We also hope that the entrance of the States in action will help bring this war to an end in not too long a time . . .
A very serious influenza epidemic has come from the front and does a good deal of harm in Switzerland. Since its beginning in July there are several hundreds of deaths here. We are looking forward to a rather dark future. The moral influence of the Bolshevik government is progressing in Europe, one can feel it here very much . . . I am more than sorry to see that everything that bears the name of Kocher is by and by assimilated by his successor, even the Kocher artery clamps! Evidently in a small country the mind is not as free, as in a large one. I am sorry to say so for old free Switzerland . . . My mother sends her kindest regards she is just now recovering from pneumonia, which kept her in bed over a month . . .
We have had nothing from Cushing. I am sure many letters have been lost.
I thank you for all your sympathy and sincerely hope that you will keep up your valuable friendship for us . . .

Yours always sincerely,"

Albert Kocher

In 1919 Halsted had become quite ill with recurrent attacks of cholecystitis. The illness greatly reduced his workload and his correspondence also decreased. The last letter he was to write to the Kocher family was in November, 1919:[18]

> "Dear Kocher: November 17, 1919
>
> . . . I have been ill for about six months, but now am convalescing normally from a cholecystectomy and choledochotomy performed about three months ago by Dr. Follis, one of my assistants.
>
> I have been particularly interested in watching the results of operative treatment of ulcer of the stomach and duodenum, but feel hardly competent to express opinions except as they have been formed from experimental work and reading and watching the results of those in our clinic to whom I have assigned the gastric cases.* My operative work has been chiefly along other lines. It has been my practice, however, to excise the ulcer when feasible . . .
>
> I hope you are very well, and beg to be most kindly remembered to Mrs. Kocher and all the members of the family. Cushing is very well indeed and seems to be very happy in Boston. I presume he keeps in touch with you.
>
> Faithfully yours,"
>
> W. S. Halsted

An analysis of the correspondence between William Halsted and Theodor Kocher and his family shows a deep and abiding respect for the other's surgical talents. In addition to this professional admiration, there was a strong, personal feeling for each other. This is of interest in that both men have been described as introverts with very few close friends. Their personalities were, however, said to "sparkle" if one could surmount the outward aloofness. They lacked the variety of talents and interests, outside of medicine, of surgeons such as Billroth, Cushing or Horsley, and were never considered "well-rounded" personalities.

Certainly, one of the most difficult of historical problems is that of assigning influence, and this holds true with Halsted and Kocher. Although it is tempting to speculate on how and to what extent they might have influenced each other, and in turn how their relationship contributed to changes in the world of surgery, this would be a futile historical task. Instead of idle speculation, it is best to say that they indeed did have a very "exquisite friendship which was full of interest", and unique in its own special way.

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* At the end of his surgical career Halsted and his assistants had begun to investigate the patho-physiology of gastric and duodenal ulcers, however, no manuscripts were prepared on this subject prior to his death.

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Colonoscopy and the Management of Polyps Containing Invasive Carcinoma

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Experiences with 565 colonoscopic polypectomies and 91 colonic and rectal resections containing infiltrating carcinoma in polyps are reviewed. A plan of management based on pathologic study of resected polyps is formulated to avoid further unnecessary surgery. It was concluded that: (1) Tubular adenomas containing invasive carcinomas have a low incidence of metastatic node involvement. This incidence is related to the depth of carcinomatous involvement. Resection of these polyps with a margin free of carcinoma constitutes definitive and adequate treatment, and that (2) Villous adenomas containing invasive carcinoma have a high incidence of metastatic nodal involvement, and operative resection of the involved area of the colon is recommended, and that (3) Pedunculated tubulovillous adenomas containing invasive carcinoma behave like tubular adenomas, and the recommendations for further surgery in the patient with tubular adenomas with carcinoma apply equally well for these lesions. Sessile tubulovillous polyps tend to behave like villous adenomas, and if invasive carcinoma is demonstrated, further operation is recommended.

COLONOSCOPIC POLYPECTOMY has become the accepted treatment for most polyps of the large bowel. The management of colonic polyps which contain invasive carcinoma still remains a controversial subject.[1,3,6,10,15,17,18] It is the purpose of this paper to propose a plan of management in these cases based on microscopic characteristics so that unnecessary surgery will be avoided.

Materials and Methods

Five hundred sixty-five colonoscopic polypectomies were performed in 435 patients over a period of 45 months. Various instruments were used for this purpose, the most recent being the Olympus CFLB-2 and TCF-2. Polyps were excised by use of electrosurgical snare technique, and were recovered for microscopic examination in 477 of 565 instances. In 80 instances the polyps were small (less that 4 mm in diameter) and appeared benign; these were destroyed with electrocoagulating current. They are not included in the total polypectomy count above, and are excluded from further discussion.

The pathologic classification of the excised polyps is shown in Table 1. Seventeen polyps (13 tubular adenomas and four tubulovillous adenomas) reported to contain invasive cancer were resectioned and restudied by one of us (S.B.); the results of this are given in Table 2. The following pathologic findings were noted: type of polyp, presence or absence of carcinoma invading through the muscularis mucosa into the substance of the polyp (defined as invasive malignancy when present), and depth of invasion into the stalk. Depth of invasion of the muscularis propria of the bowel wall, and presence or absence of carcinoma within the lymph nodes were noted in those cases in which operation was also performed.

Because the number of patients having polyps with invasive carcinoma in this colonoscopy series was small, and because all patients in the series did not undergo operation, we expanded our data by including polyps which were resected at operation prior to the availability of colonoscopic polypectomy. This material included specimens of resected colons and rectums that contained polyps with invasive malignancy, and it is derived from data that constitutes a larger review of surgically resected polyps to be published. The resected specimens selected from 91 patients contained lesions less than 5 cm in diameter, since such lesions would be amenable to colonoscopic polypectomy.[20] The specimens were resectioned and studied by one of us (S.B.), and the criteria outlined above were again utilized for pathologic classification. In addition, the depth of invasion of the carcinoma into the polyp stalk was determined and defined as invasion of the upper, mid-

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Submitted for publication: February 13, 1978.

0003-4932/78/1100/0638 $00.70 © J. B. Lippincott Company

TABLE 1. *Colonoscopic Polypectomy*

Pathologic Classification	Number of Polyps
Tubular adenoma	
Benign	299
With dysplastic focus	34
With superficial carcinoma	24
With invasive carcinoma	13
Tubulovillous adenoma	
Benign	25
With invasive carcinoma	4
Villous adenoma	
Benign	13
With superficial carcinoma	3
With invasive carcinoma	1
Juvenile	4
Lipoma	2
Hamartoma	6
Hyperplastic or inflammatory	49
Not retrieved	88
Total polyps removed	565
Total polyps recovered	477

dle, or lower third of the stalk. The pathologic criteria for invasive carcinoma in 17 tubular adenomas, 22 tubulovillous adenomas, and 52 adenomas is given in Tables 3–5 respectively.

Results

The incidence of polyps containing invasive carcinoma in the colonoscopy series was 5.6% for tubular adenomas, 16% for tubulovillous adenomas, and 41% for villous adenomas.

Thirteen patients had tubular adenomas containing invasive carcinoma removed by colonoscopic polypectomy. Six of these patients underwent operation shortly after colonoscopy because a question of residual carcinoma was raised in each case. In three of these, no residual tumor was found (patients 2–4); in the other three patients, residual carcinoma was found at the polypectomy site (patients 1, 5, and 6). Two of the six pericolonic lymph nodes removed from one of these three patients contained carcinoma. The lesion in this patient (patient 6) was relatively small and confined to the bowel wall with apparent invasion of only the superficial muscularis propria, but there was definite secondary neoplasm in two pericolonic lymph nodes.

Follow-up information was obtained from five patients who had tubular adenomas containing invasive carcinoma but did not undergo operation. In one of these patients (patient 8), a carcinoma subsequently developed two years after polypectomy, the polyp being located in the sigmoid colon. The cancer occurred at a site distant from that of the polypectomy. Four years after polypectomy, carcinoma in the sigmoid colon developed in this same patient. Two other patients in this group were actively followed, including colonoscopy at one and three years respectively, with no evidence of malignancy. A fourth patient in this group has been actively followed for two and one-half years and is asymptomatic, but has not had colonoscopy. A fifth patient has not been actively followed, but when contacted, he stated that he felt well and was asymptomatic for any signs of malignancy three years after the polypectomy. Two patients were lost to follow-up (patients 12 and 13).

Four patients had tubulovillous adenomas containing invasive carcinoma removed at the time of colonoscopy. Two of these underwent operation for this reason, and in one residual tumor was found at the site of polypectomy (patients 14 and 15). The other two patients in this group have been actively followed for four months

TABLE 2. *Colonoscopic Polypectomy Polyps with Invasive Carcinoma*

Patient No.	Pathologic Type	Polyp Diameter	Location	Other Polyps Present	Stalk Invasion
1.	Tubular adenoma	1.3 cm	Sigmoid	No	Yes
2.	Tubular adenoma	1.2 cm	Sigmoid	No	Yes
3.	Tubular adenoma	1.5 cm	Sigmoid	No	Yes
4.	Tubular adenoma	0.7 cm	Descending colon	3	No
5.	Tubular adenoma	1.0 cm	Sigmoid	No	Yes
6.	Tubular adenoma	1.1 cm	Sigmoid	4	Yes
7.	Tubular adenoma	1.0 cm	Sigmoid	3	Yes
8.	Tubular adenoma	1.3 cm	Sigmoid	4	Yes
9.	Tubular adenoma	2.7 cm	Sigmoid	No	?
10.	Tubular adenoma	2.0 cm	Descending colon	3	Yes
11.	Tubular adenoma	1.5 cm	Sigmoid	3	No
12.	Tubular adenoma	1.5 cm	Sigmoid	1	No
13.	Tubular adenoma	1.0 cm	Sigmoid	No	Yes
14.	Tubulovillous adenoma	3.0 cm	Hepatic flexure	No	Yes
15.	Tubulovillous adenoma	1.5 cm	Sigmoid	1	No
16.	Tubulovillous adenoma	1.5 cm	Rectum	2	Yes
17.	Tubulovillous adenoma	1.5 cm	Sigmoid	2	Yes

Polyp diameter = average of 3 dimensions. ? = uncertain.

TABLE 3. *Pathologic Criteria in 17 Resected Specimens Containing Tubular Adenomas with Invasive Carcinoma*

Carcinomatous Involvement	No. Specimens	No. Containing Positive Lymph Nodes
Confined to head	1	0
Upper third stalk	4	0
Middle third stalk	1	0
Lower third/base stalk	5	0
Inner half muscularis propria	1	0
Outer half muscularis propria	1	0
Extension beyond serosa	4	1*
Total	17	1

* This lesion was a carcinoma extensively replacing a tubular adenoma.

and four years respectively, and no evidence of carcinoma has been found.

In only one of the 17 patients with tubular adenomas from the surgically resected group (Tables 3–5) was there metastatic node involvement, and in this patient, the carcinomatous changes extended well beyond the serosa and the bulk of the polyp was replaced by tumor. Ten of the tubulovillous polyps were pedunculated and in none of these was there metastatic node involvement. In sessile lesions of the tubulovillous type, lymph node involvement with carcinoma was present in four of 12 patients. For villous adenomas (Table 5), size was not predictive of the presence or absence of lymph node involvement. Lesions containing only microfoci of invasion were not associated with lymph node metastasis. Once the invasion progressed beyond the submucosa, the incidence of metastatic node involvement increased.

Discussion

The overall incidence of invasive malignancy for tubular adenomas is reported to be about 4%.[1,3,5–8,10–12,17,18] Recommendations for management of these polyps vary widely. Welch et al.[18] advocate radical excision in every case of polyp; other authors, such as Turnbull et al.[17] propose more conservative treatment. Many authors favor radical operation in cases of invasive malignancy without reference to the depth of carcinomatous invasion.[1,3,10,11,12,18] Others advise radical resection if the lesion is highly undifferentiated or the carcinoma extends to the base of the stalk.[8,14,20]

Following colonoscopic polypectomy, Berci and Morgenstern[4] found no residual tumor in four patients with invasive malignancy in a polyp who subsequently had surgical resections. Wolff and Shinya[20] had 11 patients in whom subsequent colonic resection was undertaken. In three of these, polypectomy was incomplete and residual carcinoma was noted at the time of operation. In the other eight, no residual tumor was found. They recommended subsequent colectomy on the basis of this experience, only if the polypectomy is incomplete or if the plane or resection approximates an area of carcinoma.

Since there is an increasing number of colonoscopic polypectomies being performed, it becomes vitally important to establish criteria for those lesions which will require surgery. On the basis of our experience with colonoscopy and the results of pathologic study of resected colonic specimens containing polyps with invasive malignancy, the following plan is recommended where invasive malignancy is found in colonoscopically resected polyps.

From our data and that of others,[4,10,14,20] it would appear that tubular adenomas containing invasive carcinoma confined to the head of the polyp or upper part of the stalk rarely have nodal involvement. Thus, if the tubular adenoma containing malignant cells can be totally excised without cutting through a carcinomatous portion of the tumor, adequate and definitive treatment has been achieved. This applies to the stalk as well as the head of the polyp. If the margin of resection is through a carcinomatous portion of the tumor (stalk or head), then further surgical treatment is recommended because of the indeterminate actual level of invasion of the malignancy and the possibility of residual carcinoma. It would also seem logical to recommend that operative treatment be considered if angioinvasion or

TABLE 4. *Pathologic Criteria in 22 Resected Specimens Containing Tubulovillous Adenomas with Invasive Carcinoma*

Carcinomatous Involvement	No. Specimens	No. Containing Positive Lymph Nodes
Confined to head	3	0
Involvement upper third stalk	2	0
Involvement mid-third stalk	3	0
Involvement lower third stalk	5	0
Involvement inner half musc. propria	3	1
Extension beyond serosa	6	3
Total	22	4

TABLE 5. *Pathologic Criteria in 52 Resected Specimens Containing Villous Adenomas with Invasive Carcinoma*

Carcinomatous Involvement	No. Specimens	No. Containing Positive Lymph Nodes
Microfocus	1	0
Extension into submucosa	12	1
Extension inner half musc. propria	10	2
Extension outer half musc. propria	18	3
Extension beyond serosa	11	7
Total	52	13

lymphatic permeation is observed or also if the lesion is highly undifferentiated. Our data are too limited on these points to make firm conclusions.

The incidence of invasive malignancy in villous adenomas is approximately 30%.[8,9–10,13,18–20] Carcinomatous lymphatic involvement occurred in approximately 25% of our cases in the surgical series. This incidence increases as the tumor extends toward the serosa (Table 5). In view of the high incidence of lymphatic involvement with villous adenomas containing carcinoma, the presence of invasive malignancy should constitute an absolute indication for radical operation, unless the patient's general status contraindicates this. This plan is generally recommended by most authors.[2,3,9,13,16,18,19]

The information available regarding tubulovillous adenomas is inadequate. According to Wolff and Shinya[20] and Behringer,[3] the malignant potential of this lesion is intermediate between tubular and purely villous adenomas. In our series, it appears that the presence or absence of a stalk considerably influences the potential for deep penetration of carcinoma in these lesions. Although the number of such polyps in our series is small, it appears that pedunculated tubulovillous adenomas can be treated as tubular adenomas, and that sessile ones should be regarded as villous adenomas in terms of recommendations for surgery. Therefore, if such a lesion is pedunculated, and the margin of resection through the stalk is free of carcinoma, then the treatment has been adequate. If, however, the lesion is sessile and contains invasive malignancy, then operative resection is recommended.

Microscopic appearance thus plays a crucial role in the further management of tubular adenomas, tubulovillous adenomas, and villous tumors resected at colonoscopy. An attempt to excise the lesion in toto should be made and the recovered specimen should have accurate microscopic appraisal as outlined. Once microscopic evaluation is available, a plan of management following the above outlined recommendations will aid in avoiding unnecessary operations in cases of tubular adenomas or pedunculated tubulovillous adenomas. These represent lesions of very low malignant potential. The presence of lymphatic or vascular permeation and/or the presence of a highly undifferentiated lesion probably also constitute indications for resection. It must be mentioned that metastatic lymph node involvement can occur in the presence of focally invasive carcinoma. This is a very rare circumstance and less than 30 such cases have been reported.[14]

In dealing with sessile tubulovillous lesions or villous adenomas containing invasive malignancy, our data and that of others support the view that further surgery is indicated because of the high incidence of metastatic lymph node involvement.

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Iliac-Mesenteric-Atrial Shunt Procedure for Budd-Chiari Syndrome Complicated by Inferior Vena Caval Thrombosis

JAMES E. CHAPMAN, M.D., JOHN L. OCHSNER, M.D.

A 33-year-old woman had a diagnosis of idiopathic Budd-Chiari syndrome complicated by inferior vena caval occlusion. Conservative medical therapy failed to control the symptoms of both portal hypertension and vena caval stasis. Therefore, a prosthetic shunt was placed from the right common iliac vein to the right atrium with a side-arm to the superior mesenteric vein. She exhibited almost complete relief of symptoms and the graft was documented to be patent two weeks postoperatively. In many instances aggressive surgical therapy may help these patients who, in the past, would have been relegated to symptomatic therapy.

BUDD-CHIARI SYNDROME RESULTS from interference with the venous outflow from the liver and can exist in the presence of either intrahepatic or lower inferior vena caval obstruction. Side-to-side portacaval shunts have given successful results in patients with isolated hepatic venous thrombosis who have normal inferior vena cavas and portal veins. When Budd-Chiari syndrome is complicated by inferior vena caval occlusion either in its entire length, in its intrahepatic segment, or in its inferior portion, a standard side-to-side portacaval shunt will not provide benefit or even be feasible. Less common and more complex shunt operations have been devised for this situation, including splenoazygos, azygocaval, splenoatrial, splenopulmonary artery, mesenteric atrial shunts, and others. But to our knowledge, there has never been a report of a combined common iliac vein and superior mesenteric vein-right atrial shunt as reported here in the successful treatment of a Budd-Chiari syndrome, when the inferior vena cava was occluded and therefore not capable of receiving a shunt.

Case Report

In March of 1977 a 33-year-old Greek woman was transferred from her native country to the Ochsner Foundation Hospital for evaluation and treatment of inferior vena caval thrombosis. She had been healthy until six years before admission when there was a sudden onset of increasing abdominal girth without pain, fever, nausea, or vomiting and a bilateral, severe swelling of the legs. She did not have hematemesis, hematochezia, jaundice, or evidence of bleeding. She had no history of hepatitis, blood transfusion, ethynol intake, or cigarette smoking, and she was not taking oral contraceptives or hormones. She had been treated symptomatically with spironalactone (Aldactone) and furosemide (Lasix) and had undergone therapeutic paracentesis and liver biopsies. Treatment of the ascites was mildly successful, but the leg edema persisted. Therefore, one month before admission to this hospital, she had been evaluated with arteriograms, phlebograms, and repeat liver biopsies which were said to be consistent with hepatic vein outflow obstruction and inferior vena cava thrombosis. Other history and family history were not contributory.

On admission the patient was alert, and in no apparent distress. The blood pressure was 110/80 mm Hg; the pulse was 80 beats/min and regular. She was afebrile. The abdomen was distended with ascitic fluid and an umbilical hernia was present. There were many, large dilated veins across the lateral aspects of the abdomen and striae were present inferiorly. The liver was percussible and palpable 8 cm below the subcostal margin in the midclavicular line, but there was no tenderness. Bowel sounds were present. The spleen was palpable and there were no bruits. There was 4+ pitting edema in both legs extending up to the inguinal area with no cyanosis or clubbing. Pulses in both feet were good at both the dorsalis pedis and posterior tibial arteries. She exhibited no signs of portasystemic encephalopathy nor other neurologic findings. The initial impression was that there had been an acute inferior vena caval thrombosis six years in the past and that hepatic vein outflow block had developed, and represented Budd-Chiari syndrome with inferior vena caval obstruction.

The hematocrit was 38%; hemoglobin, 11.9 g/100 ml; WBCs, 7.9, and erythrocyte sedimentation rate 10 mm/hr (Westergren). The platelet count was 461,000/cu mm. Prothrombin and partial thromboplastin time were unremarkable. A 12 factor automated chemical analysis revealed a cholesterol of 134 mg/100 ml; albumin of 3.4 g/100 ml; alkaline phosphatase, 253 mU/ml; LDH, 288 mU/ml; normal SGOT, and a total bilirubin of 2.2 mg/100 ml. The creatinine was 0.8 mg/100 ml, and the electrolytes were normal. SGPT was 17, BSP retention was 26% at 45 minutes. Hemoglobin electrophoresis revealed normal adult hemoglobin. A chest roentgenogram was within normal limits with a prominent azygos vein. Lipid profile was within normal limits. Arterial blood gas determination revealed mild respiratory alkalosis. Urinalysis was normal.

Inferior venacavography revealed near total occlusion at the origin of the inferior vena cava with massive collateralization on both sides (Figs. 1 and 2). Selective celiac arteriography showed massive hepatosplenomegaly and the venous phase showed patent

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Submitted for publication: January 23, 1978.

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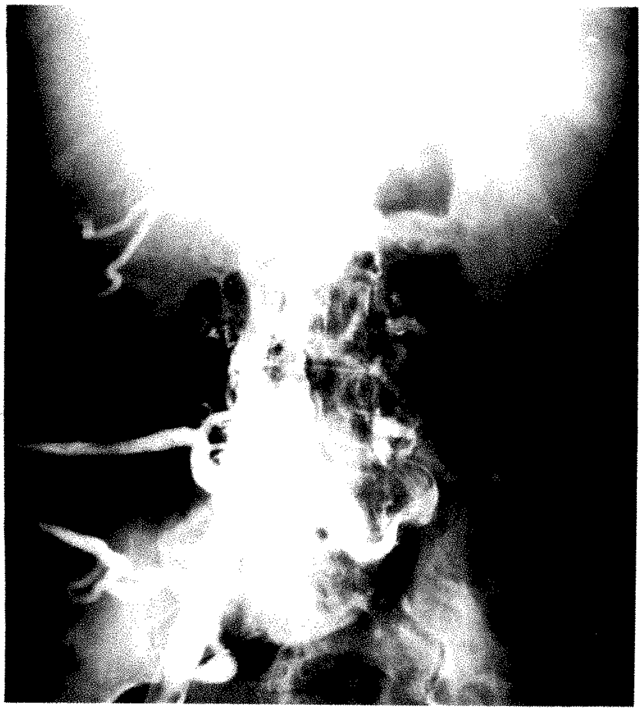


FIG. 1. Occluded inferior vena cava with paravertebral and retroperitoneal collateralization.

splenoportal veins (Fig. 3). Normal kidneys were seen on the aortic flush phase as well as patent right and left hepatic arteries.

A liver scan revealed irregular, patchy distribution in both lobes with shunting to both marrow and spleen and a greatly enlarged spleen. Superior venacavography revealed a right atrial pressure of 4 mmHg and no hepatic veins could be identified. The inferior vena cava was occluded at the level of the right renal vein and was filling from it (Fig. 4); the superior vena cava and the azygos vein were greatly dilated.

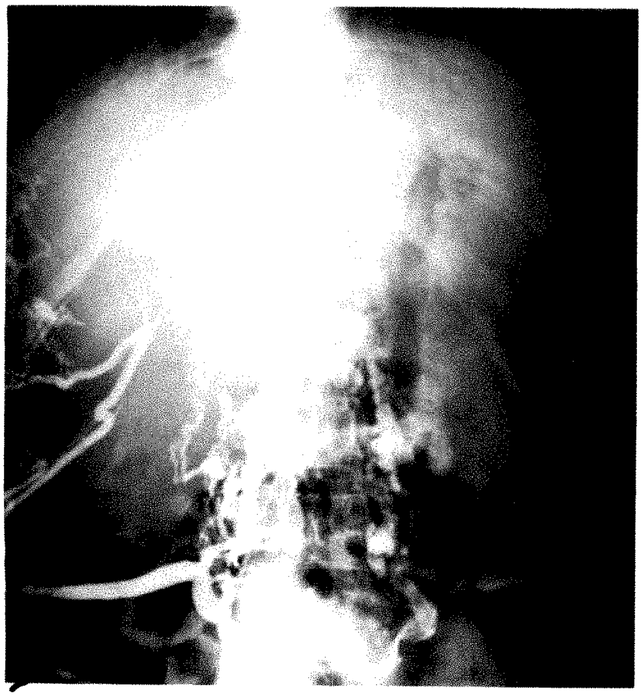


FIG. 2. Later venous phase of Figure 1.

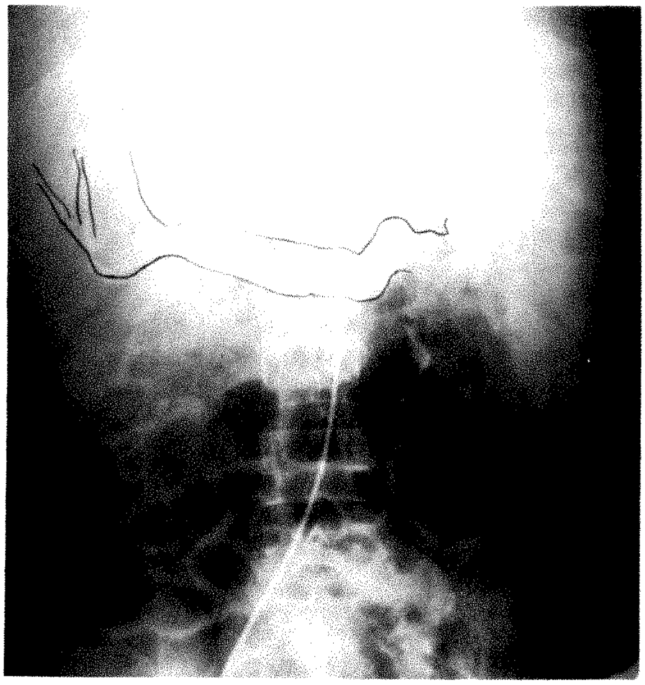


FIG. 3. Venous phase of celiac arteriogram showing normal splenic/portal vein.

A needle biopsy of the liver revealed normal appearing hepatocytes and lobules (other than dilatation of central veins) and minimal portal reaction and scarring. The diagnosis was an occluded inferior vena cava from its origin to the right renal vein, and hepatic vein thrombosis, with portal hypertension, chronic ascites, and lower extremity venous stasis. There was no evidence of either active or chronic liver disease.

Because of the severity of the symptoms, the surgical creation of a shunt was indicated. On March 13, 1977 a woven Teflon® graft, 16 mm

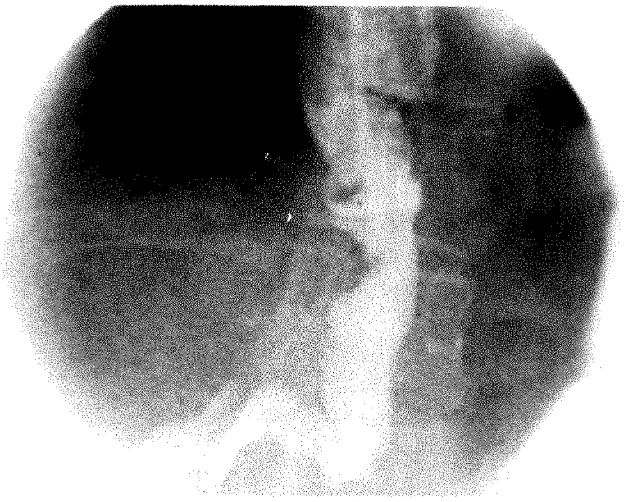


FIG. 4. Intra- and infrahepatic inferior venacavogram from superior approach demonstrating absence of hepatic venous inflow and visualization of right renal vein.

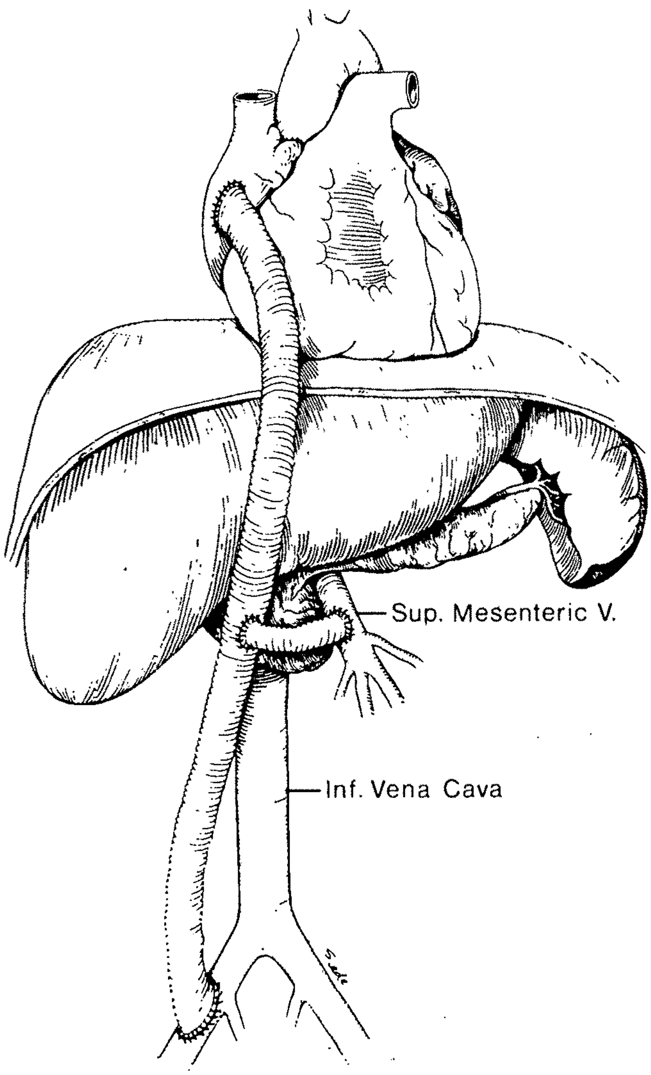


FIG. 5. 16 mm Teflon conduit interposed between the right common iliac vein and the right atrium with 10 mm Teflon side-arm to superior mesenteric vein.

in diameter, was placed end-to-side to the right common iliac vein which was found in an edematous and thickened retroperitoneal space. The graft was passed superiorly, and because of the greatly enlarged liver, it had to be directed anteriorly into the mediastinum through the space left vacant by excision of the xyphoid process of the sternum, and anastomosed to the right atrium. A 10 mm side-arm graft, 4 cm long, was placed in an H fashion from the superior mesenteric vein to the initial graft (Fig. 5). Heparin was given for anticoagulation during the installation of the vascular prosthesis. She required eight units of whole blood during the procedure.

Postoperatively, the patient did well. She was treated with anticoagulants and diuretics, and her weight decreased from 72 to 60 kg within a week of surgery. The ascites almost completely resolved and the lower extremity edema resolved entirely. On the thirteenth postoperative day a phlebogram showed the graft to be patent throughout its length (Figs. 6a and b). Doppler studies confirmed venous flow through the prosthesis from abdomen to mediastinum. Throughout the postoperative course the patient's renal functions were normal and her total protein remained within normal limits. The bilirubin which was 2.2 mg/100 ml preoperatively was 1.3 mg/100 ml on the nineteenth postoperative day. The SGOT which had been normal on admission rose to 70 mU/ml in the first week after operation and then fell to within normal limits before discharge. She was discharged on the nineteenth postoperative day, essentially free of ascites and lower extremity swelling. She was afebrile and asymptomatic. She was given sodium warfarin (Coumadin) for anticoagulation and was to continue taking spironolactone with hydrochlorathiazide (Aldactazide) 25 mg q.i.d. and potassium supplements, and to follow a low salt diet.

At last report, four months postoperatively, she was doing well and has continued to be followed-up by her physicians in Greece.

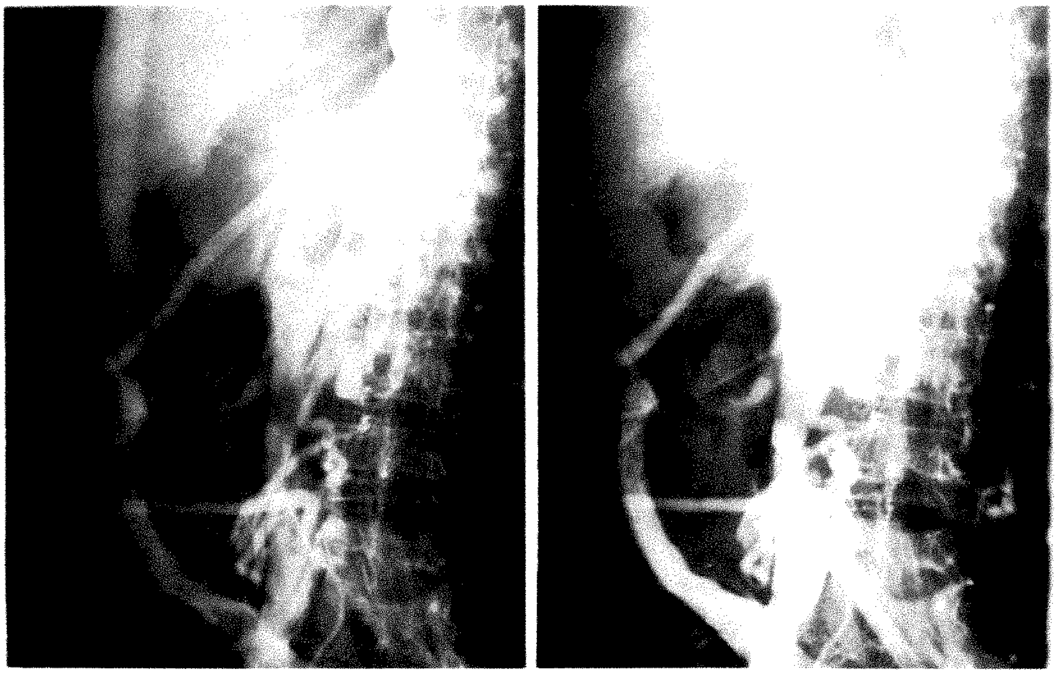
Discussion

The most common early symptom of Budd-Chiari syndrome is an increasing girth due to gross ascites and usually hepatomegaly. These symptoms may be accompanied or preceded by abdominal pain or the patient may be pain-free.[13] Jaundice is rare and usually the liver function tests are only minimally abnormal. On initial physical examination caput medusae is rarely noticed, but pitting edema of the lower extremities or the trunk has been noticed in slightly over 50% of patients.

The causes of Budd-Chiari syndrome are many and include polycythemia rubra vera, tumors in and about the liver, trauma, leukemia, sickle cell anemia, hydatid diseases, exogenous toxins, paroxysmal nocturnal hemoglobinuria, and congenital caval obstructions, as well as, a growing incidence related to oral contraceptive use.[1–4,6–8,13,18]

In Parker's classic study of 1959[13] 30% of the cases had certain, or reasonably certain, causes for Budd-Chiari syndrome, but the remaining 70% were idiopathic, and even in publications from more recent years the majority of cases are idiopathic. Lesions in the inferior vena cava were present in the majority of the idiopathic cases studied by Parker, and in a number of cases, thrombosis has been reported to involve the entire vena cava and hepatic veins, but thrombosis has also been reported to be localized from the renal veins to the diaphragm and it may or may not extend into the hepatic veins and their radicals. Occlusion of the hepatic vein ostia alone has been found in approximately 40% of all the idiopathic cases. Thrombi of different ages are nearly always present in the acute and subacute stages of the disease, and even in the majority of clinically acute cases, completely fibrosed lesions can be found. Thus, in all but the final stages of the process, lesions of different hepatic veins are usually of widely varying age as judged histologically, and are located at various levels of the hepatic venous outflow. Portal vein thrombosis can be seen in 20% of these cases.

Diagnostic aids include radiocolloid liver scans,



FIGS. 6A. Oblique view of postoperative phlebogram demonstrating graft patency. 6B. Later injection phase.

which usually show central localization of the colloid. The central localization is explained by the compensatory hypertrophy of the caudate lobe because of its more efficient perfusion and outflow which is usually not destroyed in primary hepatic vein thrombosis.[19] The narrowing and distortion of the inferior vena cava due to compression by the caudate lobe will often give a typical pencil-pointing of the intrahepatic and inferior vena cava in cases uncomplicated by inferior vena caval thrombosis.

Definitive preoperative diagnosis may require both inferior and superior venacavography, as well as abdominal and celiac axis arteriography, since other diseases such as right-sided heart failure, constrictive pericarditis, membranous obliteration of the inferior vena cava, and tumor thrombus in hepatic veins or inferior vena cava may simulate Budd-Chiari syndrome.[20] Japanese authors emphasize that simultaneous superior and inferior venacavography is necessary if one is not to miss the inferior vena caval membranes which are said to be the most common cause of Budd-Chairi syndrome among the Japanese population.[6-8,18] The celiac arteriogram is a necessary preoperative study in that any contemplation of shunting procedure requires demonstration of the anatomy as well as the adequacy of the hepatic arterial inflow. The splenoportogram done indirectly from the celiac arteriogram will reveal the presence and adequacy of the contributories to the portal vein which is necessary knowledge especially when shunts other than side-to-side are contemplated. Obviously, right heart catheterization may be useful and an attempt is usually made to cannulate the hepatic vein ostia themselves, which may or may not be possible even with a clinical picture consistent with complete hepatic vein thrombosis. In many cases occlusion of the hepatic veins does not occur at the ostia, but in more proximal, medium, hepatic vein channels such that the ostia themselves may appear normal radiologically and may even give a reading for hepatic wedge and free hepatic vein pressure measurements.

The natural history of the disease dictates that, when a patient fails to improve on adequate medical therapy, a decompressive shunt is the only chance for relief of symptoms and protection from the effects of chronic portal hypertension. Langer's review of the results of treatment in 55 cases published since 1959 emphasized the importance of definitive surgical therapy and recommended it for all but the most rapidy resolving cases.[9] Five of 14 patients given definitive operations died, but the other 9 improved; whereas 29 of 41 medically treated patients died, and only 7 improved.[9]

Most of the reported patients successfully treated with shunts are those whose disease was not complicated by concomitant inferior vena caval obstruction. Side-to-side portocaval or mesocaval shunts have been relatively successful in these less complicated situations.[16,14]

For patients who have concomitant inferior vena caval obstruction more complex and less successful shunt operations have been devised. Hales and Scatliff[5] in 1966 treated a man with chronic Budd-Chiari syndrome and inferior vena caval obliteration with a Dacron® Y-graft placed between the right atrium superior mesenteric vein, and the right internal iliac *artery*, crossing the diaphragm in a trough through the anterior superior aspect of the left lobe of the liver. The gastrointestinal bleeding was eliminated postoperatively but the patient died on the tenth postoperative day. The prosthetic graft and the anastomoses were all widely patent at autopsy. Sen et al.[18] in 1967 treated a patient with portal hypertension and suprahepatic vena caval occlusion with a Dacron shunt from portal vein to the right atrium; however, the patient died two weeks following the operation. At autopsy the shunt was found to be patent. Lataste and Albou in 1971 reported an unsuccessful attempt at splenomesenteric-atrial bypass.[10] Leger et al. in 1966 utilized a Teflon prosthetic implant from the splenic vein to the left pulmonary artery which failed, and in another patient, attempted a splenic vein to right atrial shunt.[11] O'Hara et al. in 1963 were probably the first to report the cavoatrial shunt but their results had not been good.[12] Both azygocaval and splenoazygos shunts have been used with occasional success.[21,15] However, to our knowledge a shunt from the common iliac vein to the right atrium with a side branch to the superior mesenteric vein has never before been reported. Such a shunt was necessary for our patient to alleviate the symptoms of vena caval occlusion. The patient's onset and clinical course were characteristic of the Budd-Chiari syndrome and the thrombosis of the inferior vena cava was certainly a related event. The objective and subjective improvement was dramatic and should encourage more optimism in the surgical treatment of such patients.

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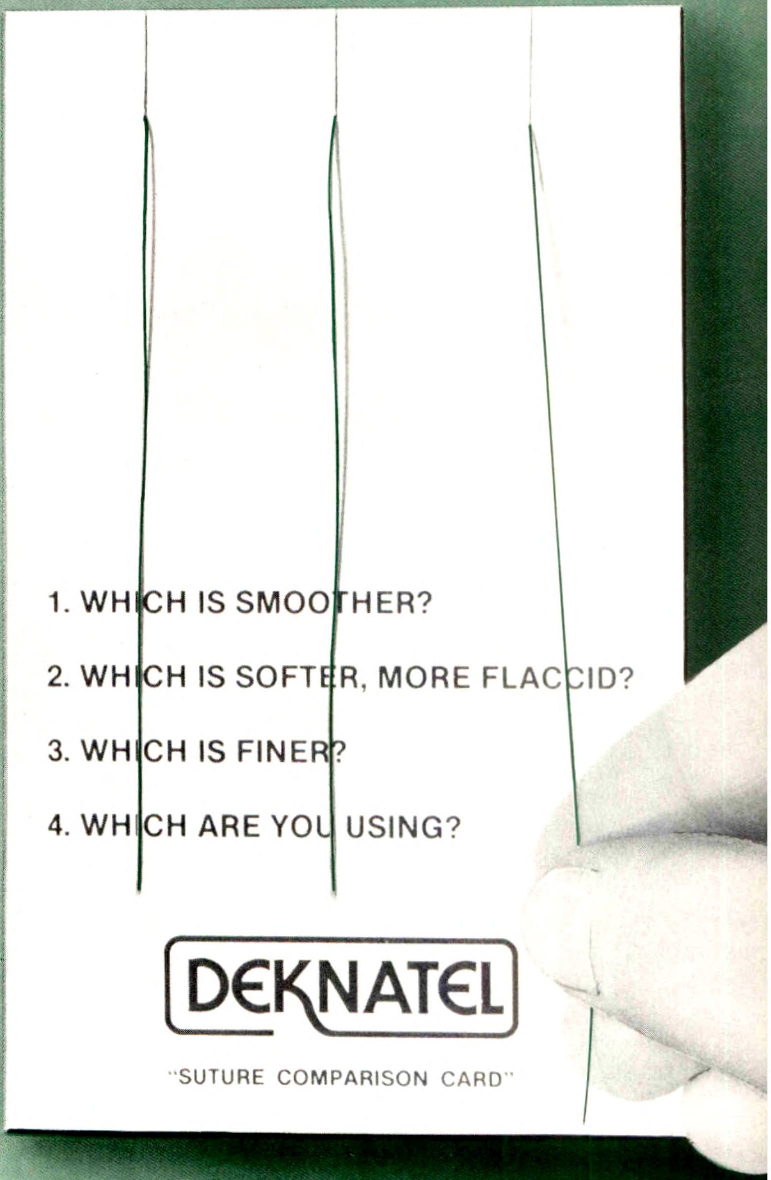

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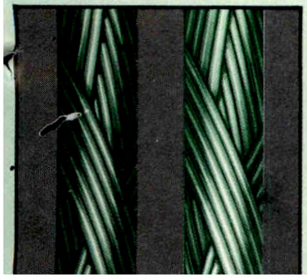

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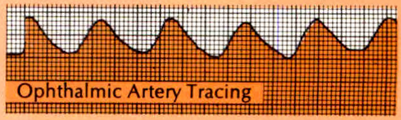

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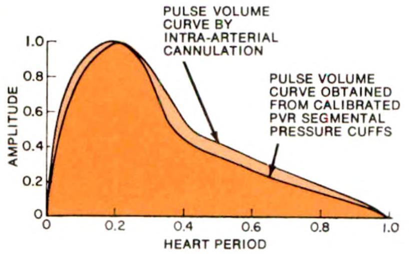
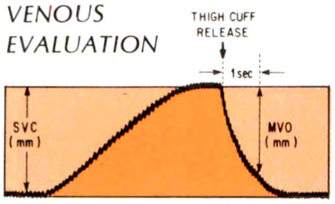


Comparison of pressure contours obtained with the PVR and direct cannulation of the common femoral artery.



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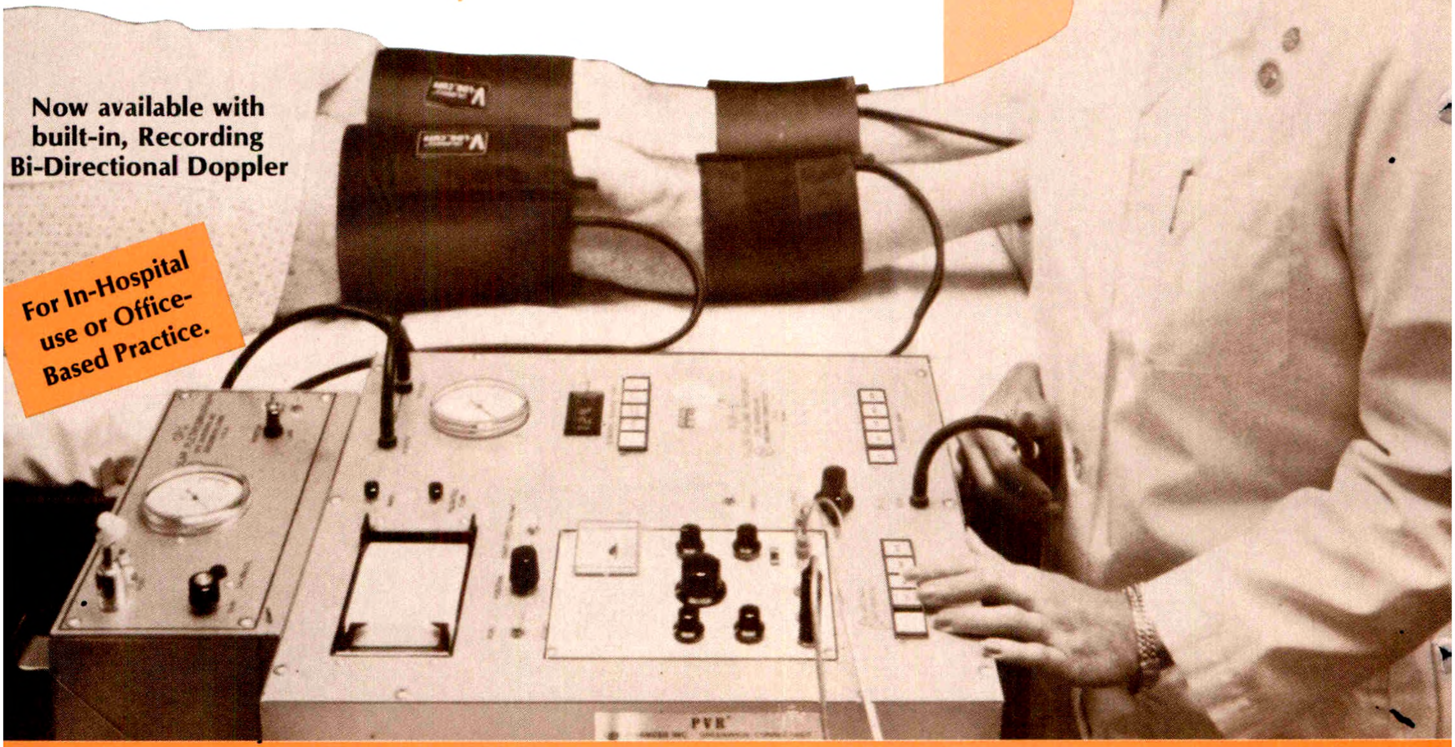
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Greenwich, Connecticut 06830 U.S.A.

Can any hospital antibiotic be this good?

"...[Amikacin] also has the remarkable property...of being inactivated by only one aminoglycoside-inactivating enzyme."

Yow MD, An Overview of Pediatric Experience with Amikacin. *Am J Med* (special issue): 167-171, June 1977.

"The standard dose of amikacin usually produces a peak serum concentration which is five times the MIC of most pathogens."

Trenholme GM, McKellar PP, Rivera N, et al: Amikacin in the treatment of gram-negative pneumonia. *Am J Med* 62:949-953, June 1977.

"When these 17 patients, who had previously failed to respond to gentamicin therapy, were treated with amikacin, the response was favorable in 16."

Tally FP, Gorbach SL: Review of 152 patients with bacteremias treated with amikacin. *Am J Med* 62:940-944, June 1977.

"In general, against many gram-negative bacterial species, amikacin is the most effective antibiotic currently available for use..."

Marget W, Reindke B, Versmold H: use of amikacin in a hospital for children: Microbiological and clinical studies. *J Infect Dis* 134(suppl): S412-S419, November 1976.

"...in combination with high doses of carbenicillin or ticarcillin in patients with renal failure, there is less chance of interaction...when it is amikacin."

Holt HA, Broughall JM, McCarthy M, et al: Interactions between aminoglycoside antibiotics and carbenicillin or ticarcillin. *Infection* 4 (2):107-109, 1976.

"Despite extensive use over a three year period...we have not encountered additional instances of Enterobacteriaceae resistance to amikacin therapy..."

Doughty SC, Martin RR, Greenberg SB: Treatment of hospital-acquired infections with amikacin. *Am J Med* (special issue): 53-57, June 1977.

"Amikacin sulfate...should be the empiric agent of choice for patients with serious sepsis.

Hewitt WL, Gram-Negative Sepsis Symposium, Boston, Massachusetts, January 24, 1976.

"All isolates were inhibited by amikacin and 95% were killed by concentrations achievable in serum with recommended doses.

Leonard JM, McGee ZA, Alford RH: Gentamicin-resistant bacillary infection. *Arch Intern Med* 138:201-205, Feb. 1977.

"All serum levels obtained within three hours following a dose of amikacin exceeded the MIC's of the infecting organisms...

Pollock AA, et al: Amikacin therapy for serious gram-negative infection, JAMA 237:562-564, Feb. 1977.

"High serum levels of amikacin were obtained with no evidence of renal or ototoxicity.

Eller JJ, et al: Amikacin treatment of pseudomonas pneumonia in cystic fibrosis patients with advanced pulmonary involvement. *Am J Med* (special issue): 179-185, June 1977.

"...amikacin is effective therapy for severe gram-negative infections and is no more ototoxic or nephrotoxic than gentamicin.

Smith CR, Baughman KL, Edwards CG, et al: Controlled comparison of amikacin and gentamicin. *N Engl J Med* 296:349-353, Feb. 1977.

"...amikacin provides the physician with a better chance of obtaining therapeutic blood levels above and beyond the MIC of the organism in question.

Klainer AS, Five questions: A comparative analysis of the newest aminoglycoside, film Sept. 1977.

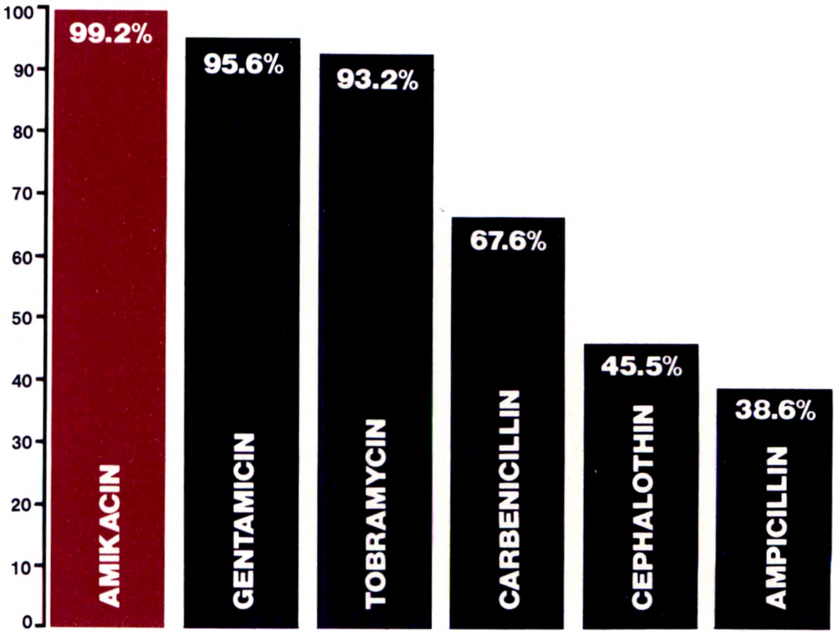
"...only one enzyme found in gram-negative bacteria affected amikacin potency, whereas six enzymes affected gentamicin and sisomicin; five, kanamycin and tobramycin and four, netilmicin.

Price K, et al: Amikacin activity, *Am J Med* (special issue) 14-24 June 1977.

Take a look at

In-vitro superiority against today's hospital pathogens

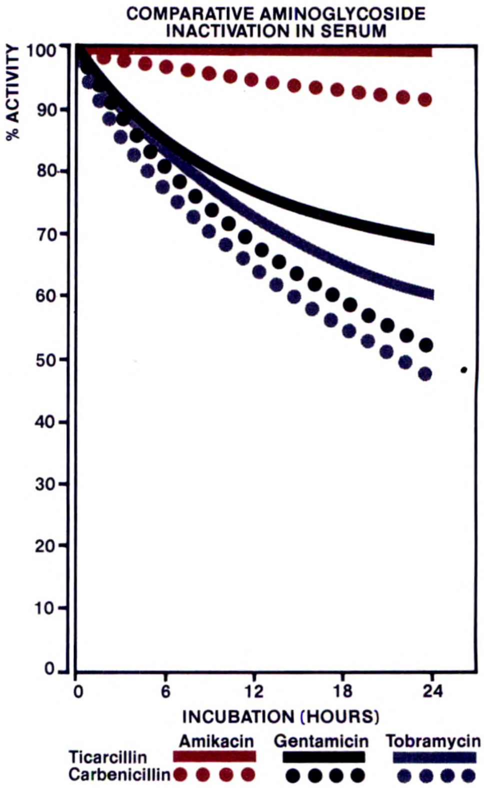
Against 409 bacterial isolates, Amikin® (amikacin sulfate) activity was compared to leading injectable antibiotics. *None* of these agents inhibited as high a percentage of strains as did Amikin.



Susceptibility determined by the agar dilution test method, data on file, Bristol Laboratories. Caution, *in vitro* data cannot be directly correlated to clinical effectiveness.

Least inactivated in combination

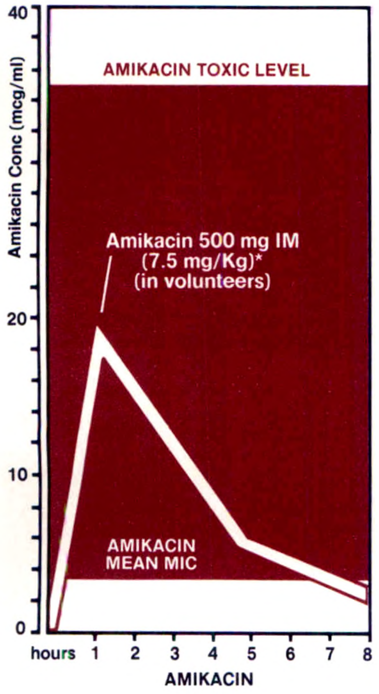
When carbenicillin or ticarcillin is combined *in vitro* with ordinary aminoglycosides, a significant reduction in aminoglycoside activity may occur. Virtually uneffected in the presence of ticarcillin, Amikin is also minimally compromised by carbenicillin...while other aminoglycosides may lose up to 50% of their activity in patients with renal impairment!

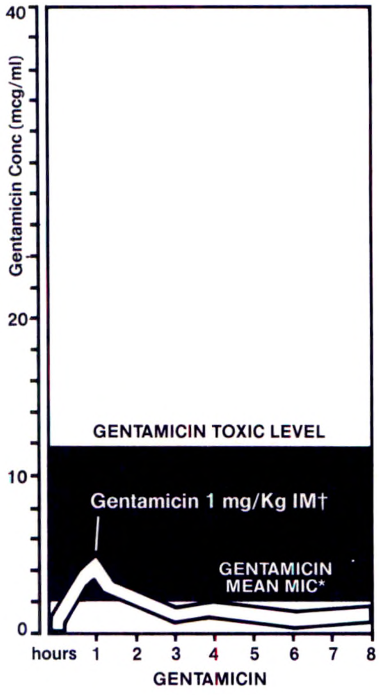


Adapted from Holt HA, Broughall JM, McCarthy M, et al: Interactions between aminoglycoside antibiotics and carbenicillin or ticarcillin, *Infection* 4(2):107-109, 1976.
Caution, *in vitro* data cannot be directly correlated to clinical effectiveness.

AMIKIN® IM IV
AMIKACIN SULFATE

the numbers!





Broader therapeutic index

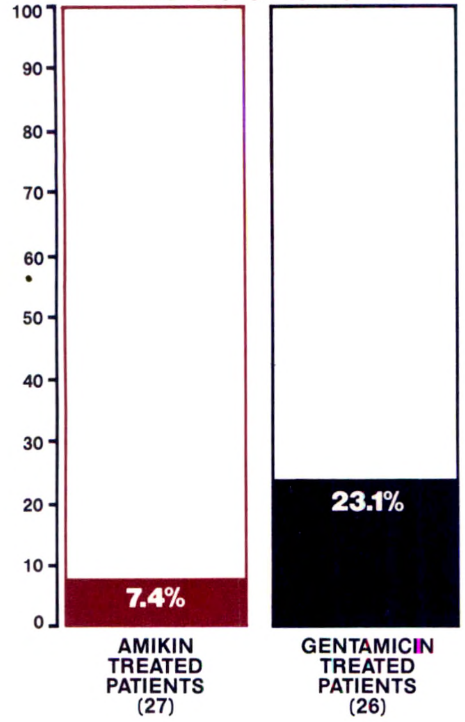
Amikin's Toxic-to-Therapeutic Index (ratio of toxic serum level to Mean MIC) is three times greater than the next leading aminoglycoside!

Because individual patient serum levels may vary from statistical averages, Amikin's broader margins reduce the risk of subtherapeutic or toxic dosage.

*Data on file, Bristol Laboratories

†Concentration curves adapted from: Winter RE, Litwack KD, Hewitt WL: *J infect Dis* 124 (suppl): 590-595, December 1971

COMPARISON OF OTO- AND NEPHROTOXICITY AS DETECTED BY AUDIOMETRIC & RENAL FUNCTION MONITORING



Well tolerated

As with other aminoglycosides, adverse auditory and renal reactions may occur at higher doses, reversible in some instances. But, in a study comparing the oto- and nephrotoxicity of amikacin and gentamicin among 53 monitored patients, Amikin demonstrated a significantly reduced side effects risk. (Other published studies have shown little or no differences in toxicity).

Special Note: In Amikin clinical trials, hearing loss was rarely clinical and usually an audiogram was needed to identify such a loss. Adverse renal reactions due to Amikin usually consisted of elevations of serum creatinine and/or BUN, which were usually reversible.

Adapted from Lerner SA, Seligsohn R, Rudd R and Matz GJ. Comparative clinical studies of ototoxicity and nephrotoxicity of amikacin and gentamicin. Proceedings 10th International Congress of Chemotherapy, Zurich, Switzerland Sept. 1977.

Probably today's most important hospital antibiotic.

Please see full prescribing information following.

AMIKIN® IM IV
AMIKACIN SULFATE

Probably today's most important hospital antibiotic.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
AMIKIN® (amikacin sulfate)
For complete information, consult Official Package Circular. (1) AMIKIN 5/24/76

Warnings:
Patients treated with aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use.

Ototoxicity, both auditory and vestibular, can occur in patients treated at higher doses or for periods longer than those recommended. The risk of amikacin-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing.

The ototoxicity potential of amikacin in infants is not known. Until more safety reports become available, amikacin should be used in infants only in those specific circumstances when susceptibility testing indicates that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed closely for evidence of toxicity.

Aminoglycosides are potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Evidence of impairment in renal, vestibular or auditory function requires discontinuation of the drug or dosage adjustment.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 35 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells and casts.

Concurrent and/or sequential use of topically or systemically neurotoxic or nephrotoxic antibiotics should be avoided.

Amikin should not be given concurrently with potent diuretics.

Usage in Pregnancy: Amikin should be used in pregnant women only when clearly needed.

Indications:
Serious infections due to susceptible strains of Gram-negative bacteria including pseudomonas sp., *E. coli*, indole-positive and indole-negative proteus sp., providencia sp., klebsiella-enterobacter-serratia sp., and acinetobacter sp. Culture and sensitivity studies should be performed.

Clinical studies have shown Amikin to be effective in bacteremia and septicemia (including neonatal sepsis); in serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft-tissue; intra-abdominal infections (including peritonitis); and in burns and post-operative infections (including post-vascular surgery). Clinical studies have shown Amikin (amikacin sulfate) also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Amikin injectable, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

Bacteriologic studies should be performed to identify causative organisms and their susceptibilities to amikacin. Amikin may be considered as initial therapy in suspected Gram-negative infections and therapy may be instituted before obtaining the results of susceptibility testing. Clinical trials demonstrated that Amikin was effective in infections caused by gentamicin and/or tobramycin resistant strains of Gram-negative organisms, particularly *Proteus rettgeri, Providencia stuartii, Serratia marcescens* and *Pseudomonas aeruginosa.* The decision to continue therapy with the drug should be based on results of the susceptibility tests, the severity of the infection, the response of the patient and the important additional considerations contained in the "Warning" box above.

Amikin has also been shown to be effective in staphylococcal infections and may be considered as initial therapy under certain conditions in the treatment of known or suspected staphylococcal disease such as, severe infections where the causative organism may be either a Gram-negative bacterium or a staphylococcus, infections due to susceptible strains of staphylococci in patients allergic to other antibiotics, and in mixed staphylococcal/Gram-negative infections.

Amikacin may be indicated in the treatment of neonatal sepsis when susceptibility testing indicates that other aminoglycosides cannot be used. In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin-type drug may be indicated because of the possibility of infections due to Gram-positive organisms such as streptococci or pneumococci.

Contraindications:
A history of hypersensitivity to amikacin.

Warnings:
See "Warning" box above.

Precautions:
Amikin is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymycin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Adverse Reactions:
Ototoxicity—See "Warning" box.

Nephrotoxicity—Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other—Skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

Dosage and Administration:
The usual I.M. or I.V. dose with normal renal function is 15 mg./Kg./day divided into 2 or 3 equal doses administered at equally-divided intervals. For the heavier individual (greater than 100 Kg.), the total daily dose should not exceed 1.5 Gms. per day.

When amikacin is indicated in newborns (see box "Warning"), it is recommended that a loading dose of 10 mg./Kg. be administered initially to be followed with 7.5 mg./Kg. every 12 hours.

The usual duration of treatment is 7 to 10 days. The total daily dose by all routes of administration should not exceed 15 mg./Kg./day for the average-weight person. In the unusual circumstances where treatment beyond 10 days is considered, the use of Amikin should be reevaluated and, if continued, renal and auditory functions should be monitored daily.

For patients with impaired renal function, whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval.

The solution for intravenous use is prepared by adding the contents of a 500 mg. vial to 200 ml. of sterile diluent such as Normal Saline or 5% Dextrose in Water or any other compatible solution.

The solution is administered over a 30- to 60-minute period.

Supplied:
Rubber-capped vials as a ready-to-use sterile aqueous solution: 100-mg., 500-mg., and 1.0-Gm. vials.

BRISTOL®
BRISTOL LABORATORIES
Division of Bristol-Myers Co.
Syracuse, New York 13201

COLACE®
dioctyl sodium sulfosuccinate

Colace means escape—from laxative stimulation, from laxative harshness, from laxative habit. Colace gently helps soften stools for easy, painless, unstrained elimination. It's the great laxative escape, from infancy to old age. Available in 100 and 50 mg. capsules. Syrup or liquid.

MeadJohnson
PHARMACEUTICAL DIVISION

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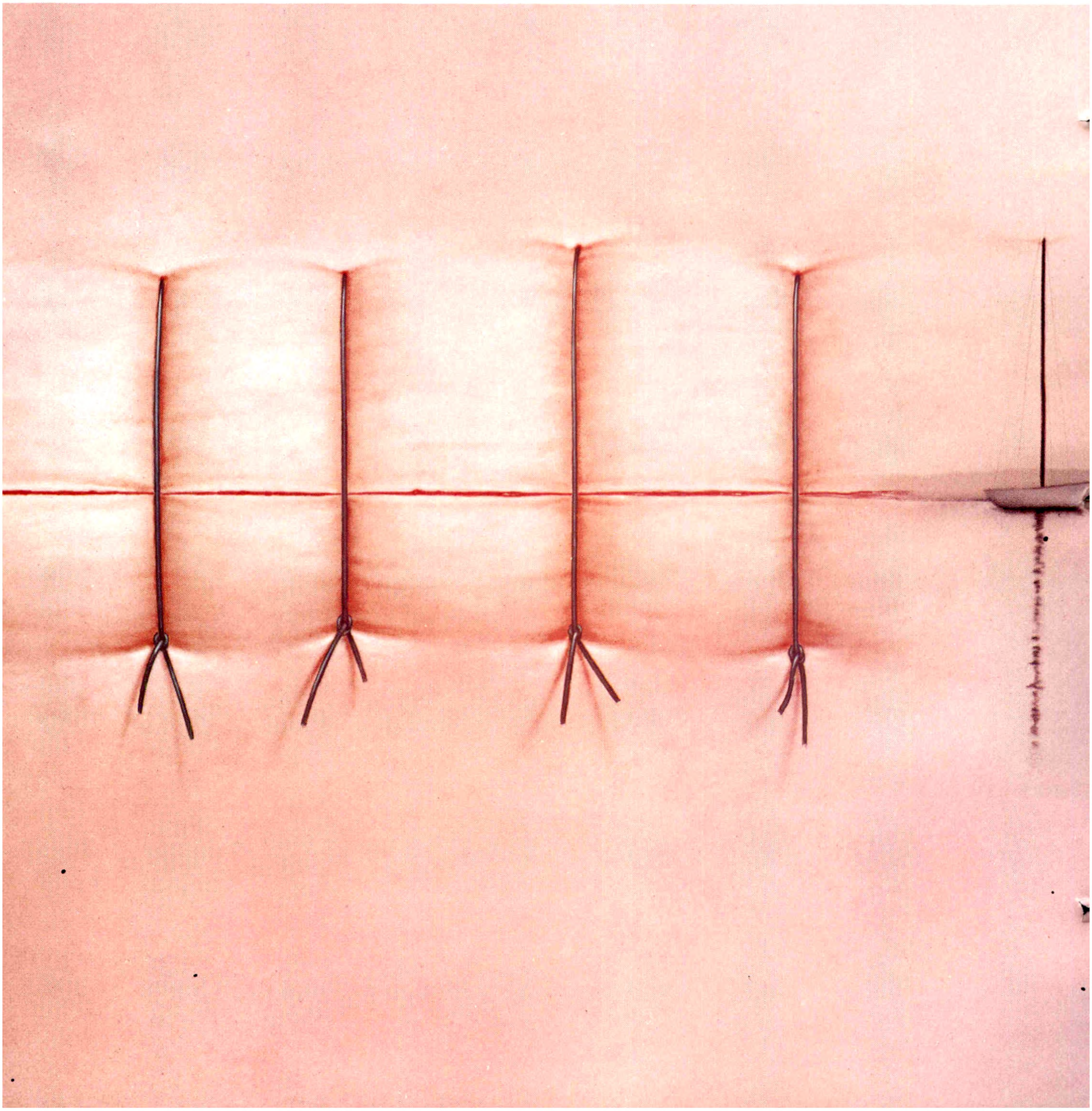
"...it has long been recognized that anxiety, tension, agitation, and apprehension are all capable of increasing pain perception..."

Halpern, L. M.: Anxiety and pain in postoperative patients. Hospital Practice *(special report) January 1977, pp 31-*

Following surgery... the perception of pain diminished



Vistaril® I.M.
(hydroxyzine HCl)

by Calm

- reduces the anxiety component of pain
- permits reduction in narcotic dosage
- controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

© 1977, Pfizer Inc.

Vistaril® I.M.

(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

**preoperatively
and
postoperatively**

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml–10 ml vials; 50 mg/ml–2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml–1 ml fill; 100 mg/2 ml–2 ml fill.

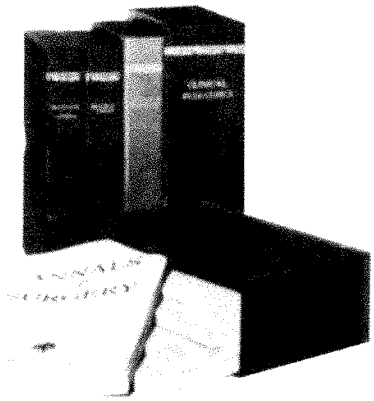
Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

Pfizer

LABORATORIES DIVISION
PFIZER INC



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Lifesaving Partnership... Against Cancer Quackery

The anguish associated with cancer is compounded by the cancer quack. False hopes—harmful delays—devastating expenses—deceptive diagnoses—loss of life—these are hazards facing the cancer patient desperate enough to seek a cancer quack.

The problem: how to divert the patient from this tragic encounter.

As medical guide, family counselor, trusted friend—you, *doctor,* play a major role in the fight against cancer quackery.

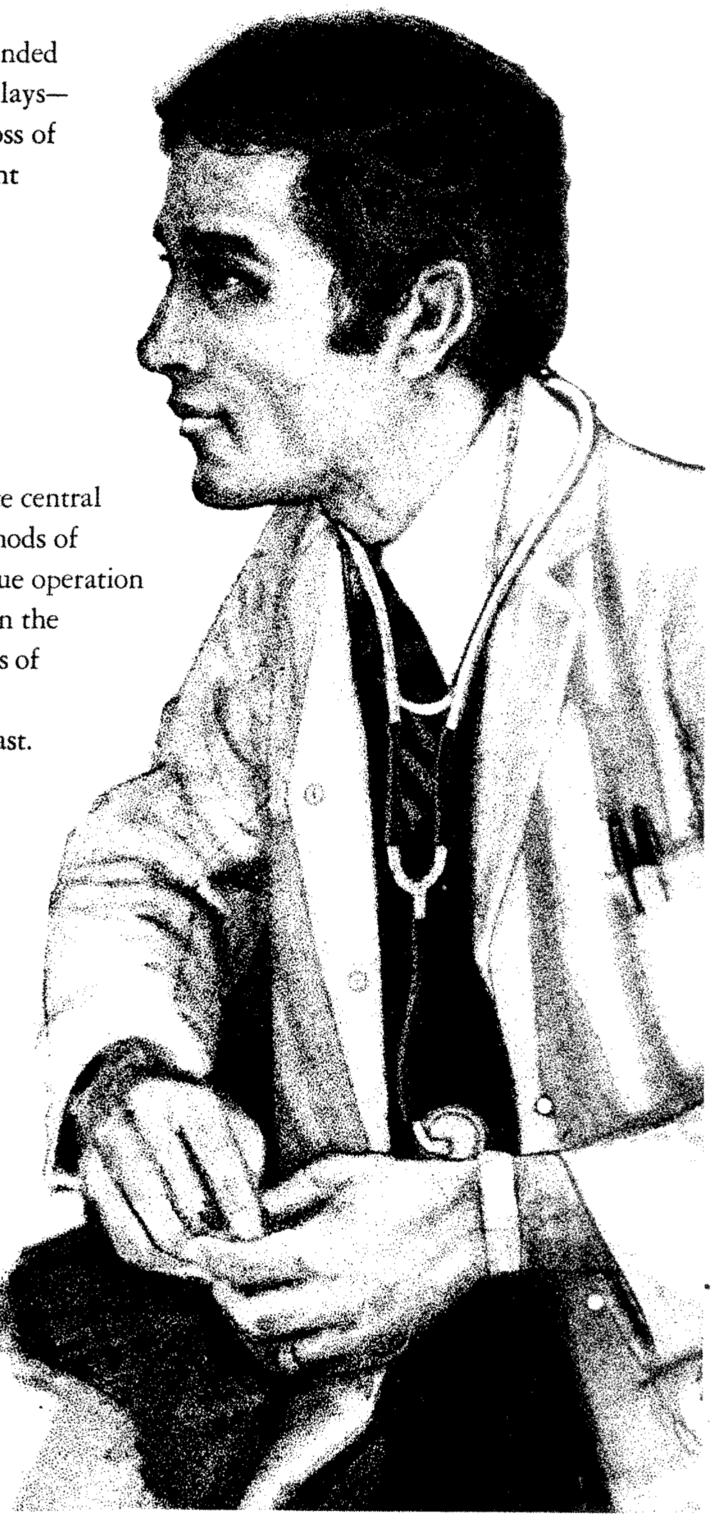
We are here to serve as your partner.

Our National Office maintains an up-to-date central clearinghouse for materials on unproven methods of cancer diagnosis and treatment. This is a unique operation and the principal source of such information in the country. Its services are widely used. Hundreds of inquiries are received and answered from all segments of the community, from coast to coast.

To trigger grass-roots action, we have formulated a model State Cancer Remedy Act designed to control the promotion and sale of unproven methods of cancer management. This has helped to inspire some 20 states to enact or consider legislation against cancer quackery—with active support from the medical community. Copies of the model act, as well as copies of laws in effect, are available through our National and Division offices.

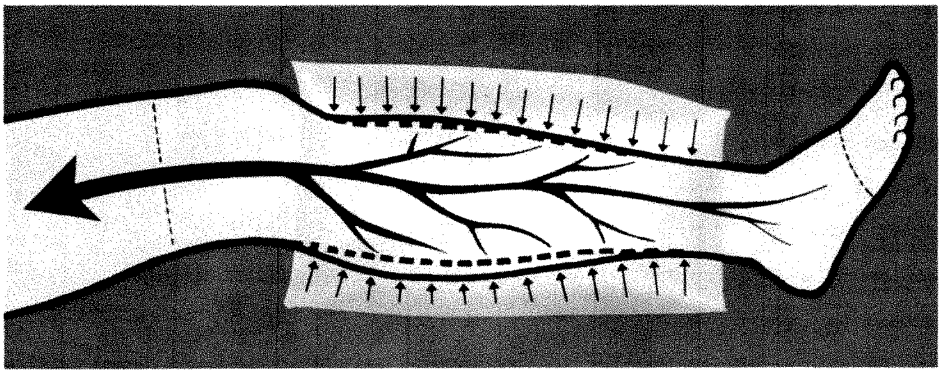
In these actions against cancer quackery, as in all our efforts against cancer, ours is a lifesaving partnership.

American Cancer Society



Up to 100,000 deaths from Pulmonary Embolism can be prevented

Now you can ambulate your patients on the table with the Venodyne® intermittent compression system.



- *Venodyne simulates calf muscle action.*
- *Venodyne is totally non-invasive and non-pharmacologic.*
- *Venodyne is simple to operate, compact, noiseless.*

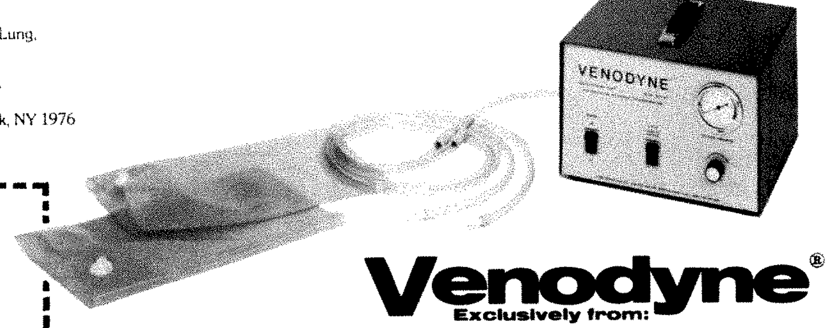
Annually about 6,000,000 adults in the United States suffer from episodes of pulmonary embolization and the mortality rate is close to 100,000 per year.[1] The deep leg veins are the source of the embolism in most patients.[2] And two-thirds of the deaths from massive embolism have been considered to be potentially preventable.[2] Additionally, it has been estimated that 50% or more of patients presenting with venous thrombosis suffer from some form of post-thrombotic syndrome by 5 to 10 years after the thrombotic event[2].

Early ambulation, leg exercises and elastic stockings have not significantly reduced the incidence of thrombophlebitic disease. Clotting normally commences before prophylactic measures have been instituted... usually while the patient is on the operating table. The various anticoagulants are the occasion of numerous contraindictions and complications.

Non-invasive, non-pharmacologic VENODYNE prophylaxis has been clinically shown to be as effective as anticoagulation, and much more effective than the various other physical methods of prophylaxis.

The VENODYNE system employs an inflatable plastic leg sleeve providing intermittent calf compression to simulate the normal calf muscle action of venous return. In essence, the system ambulates the patient on the operating table while under general anesthesia, or during any period of bed confinement. The system is safe, simple, and practical to use—and it's virtually trouble-free. Patient and nurse acceptance has been excellent.

Reprints of a number of professional papers on intermittent compression prophylaxis are available. **Write for free copies.**



1. *Cudkowicz and Sherry,* Heart and Lung, Vol 7, No 1, Jan-Feb 1978
2. *Gallus,* Venous Thromboembolism, Prevention and Treatment, Appleton-Century-Crofts, New York, NY 1976

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MA 02194 Tel. 617-449-4900

Reprints on intermittent compression prophylaxis

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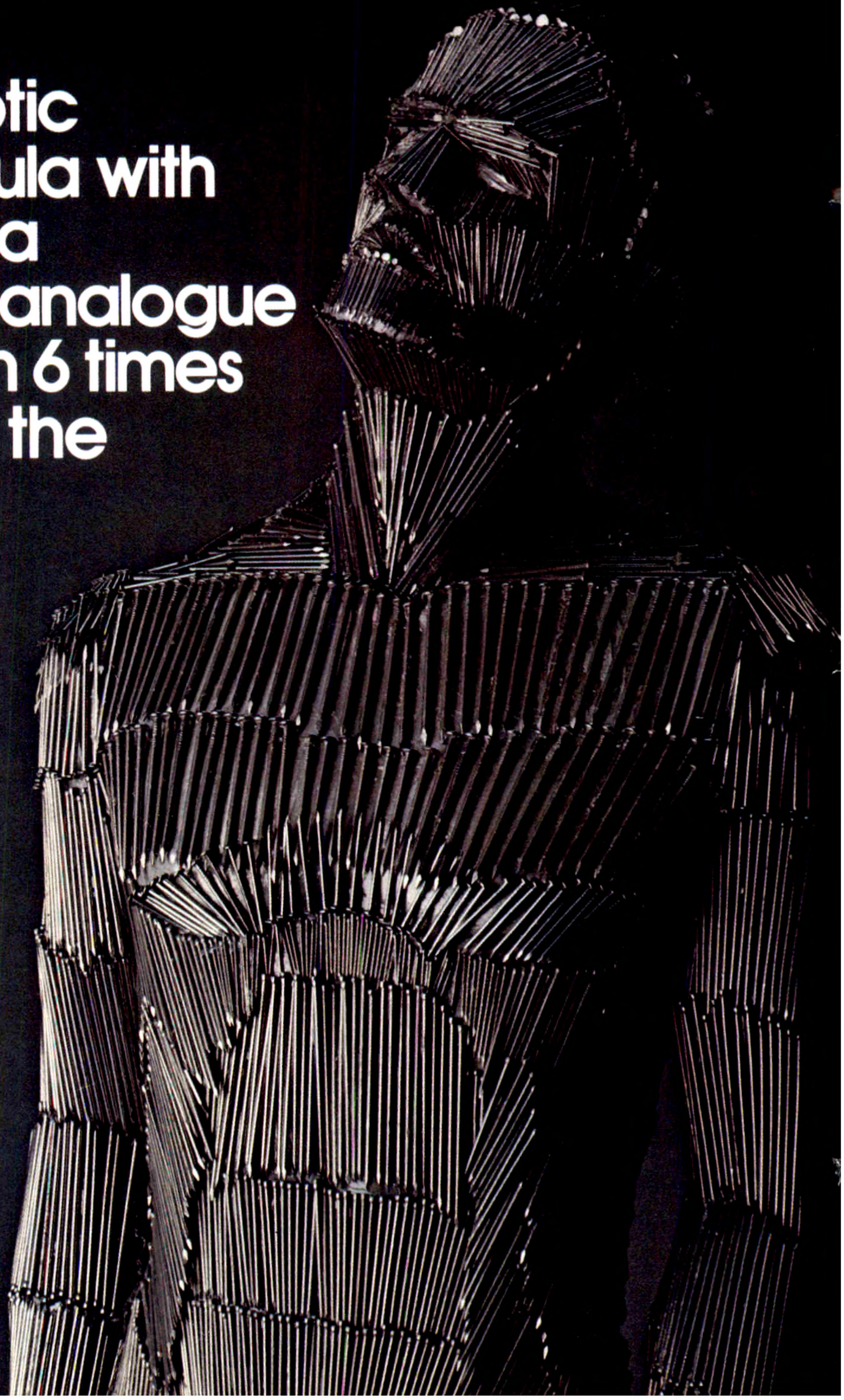
In search of Victory over pain

Knoll Pharmaceutical Company announces...

vicodin™ CIII

hydrocodone bitartrate 5 mg. with acetaminophen 500 mg.



A unique narcotic analgesic formula with hydrocodone–a semi-synthetic analogue of codeine with 6 times the potency of the parent drug

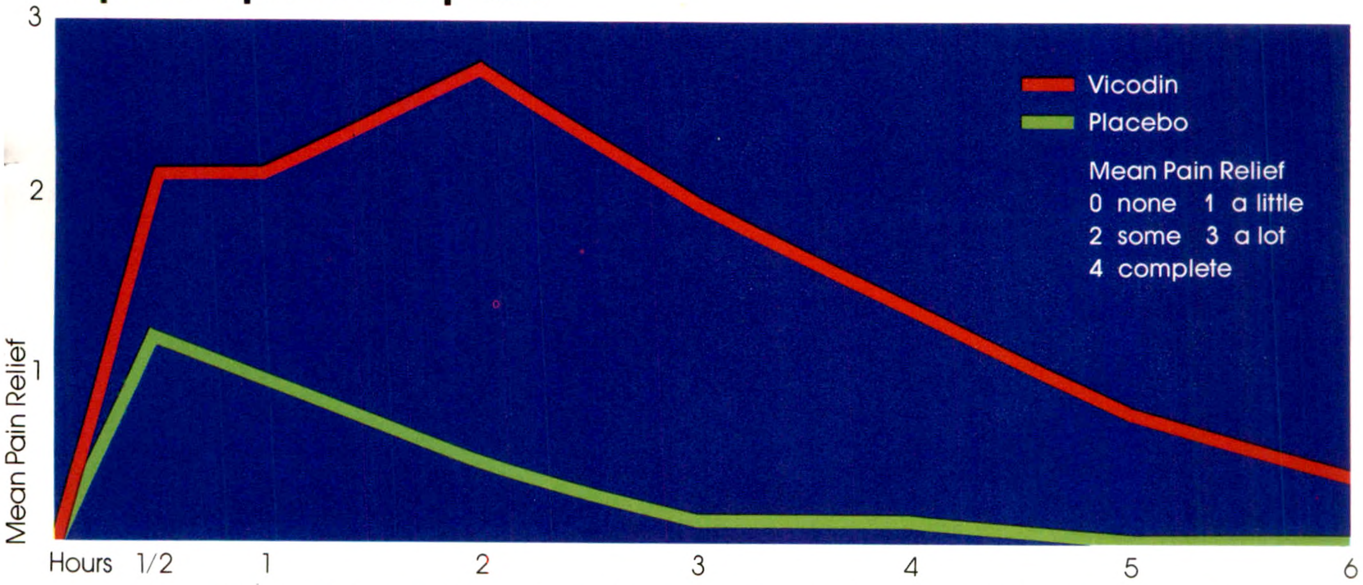
. . . combined with 500 mg. of acetaminophen for improved analgesic activity in moderate to moderately severe pain

Controlled clinical trials in patients with moderate to moderately severe pain have shown that 10 mg. of hydrocodone is approximately equivalent to 60 mg. of codeine in producing total pain relief.[1,2] In addition, 500 mg. of acetaminophen is a clearly more effective dose than the 300 mg. provided by many codeine/acetaminophen combinations.[3,4,5]

1. Data on file at Knoll Pharmaceutical Company (To be published)
2. Hopkinson, J., III: Data on file, Knoll Pharmaceutical Company (To be published)
3. Koch-Weser, J.: New England J. Med. 205:1297, 1976
4. Hopkinson, J.H., et al.: Current Therap. Res. 19:622 (June) 1976
5. Hopkinson, J.H., et al.: Current Therap. Res. 16:194 (March) 1974

A major alternative to combinations of codeine with non-narcotic analgesics

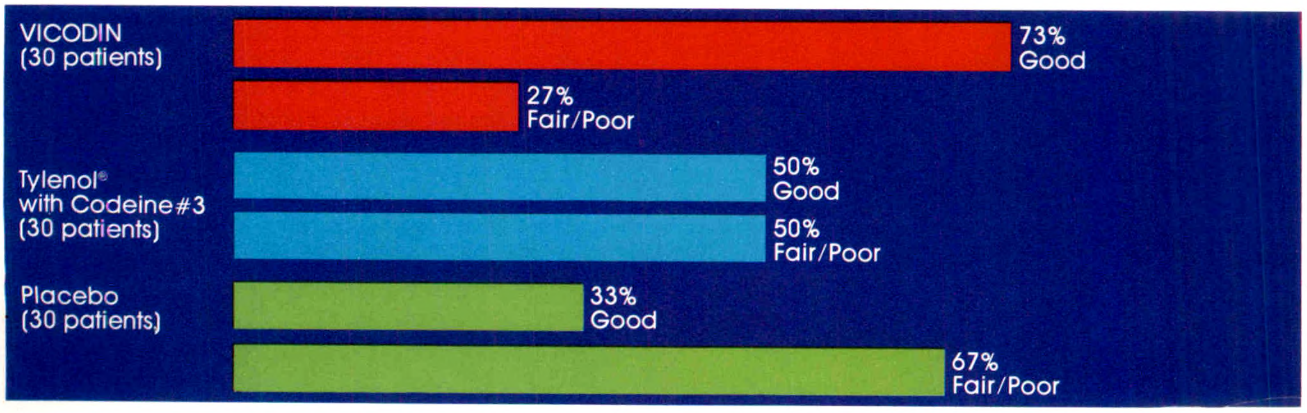
Analgesic effectiveness of VICODIN™ in post operative pain[6]



- In a placebo-controlled double-blind study[6] in patients experiencing moderate or moderately severe pain after surgery, VICODIN was administered to 8 patients and a placebo to 8 others.
- Over a 6-hour evaluation period, VICODIN showed statistically significant superiority in terms of mean pain relief over placebo at hours 2, 3, 4 and 5, after administration.
- In addition, VICODIN was statistically superior to placebo both in terms of total acceptability and total pain relief.

[6] Data on file at Knoll Pharmaceutical Company (To be published)

Analgesic response to VICODIN,™ Tylenol® with Codeine #3, and Placebo in 90 post partum patients[7]



- Three groups of 30 women each with moderate or moderately-severe post partum pain following episiotomy were treated with VICODIN, Tylenol® with Codeine #3, and a placebo.[7]
- In this controlled double-blind study, VICODIN showed statistically significant superiority over Tylenol® with Codeine #3 in terms of overall patient acceptability.

[7] Hopkinson, J., III, Study II, in press.

Tylenol® is a registered trademark of McNeil Laboratories, Inc.

vicodin™ CIII

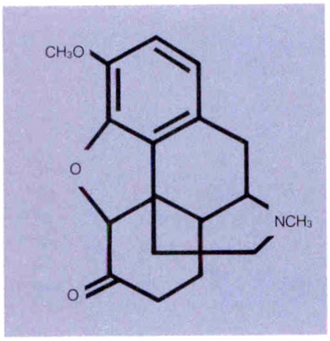
hydrocodone bitartrate 5 mg. with acetaminophen 500 mg.

The convenience of telephone prescribing and Rx refills

VICODIN™ is a schedule III narcotic.

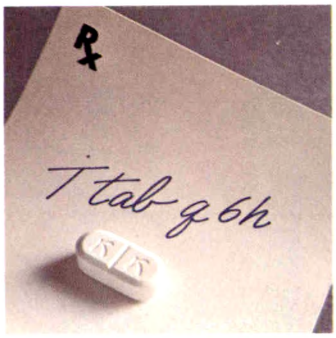
Up to 5 refills in 6 months, at your discretion, where state law permits.

And, prescribing by phone is permissible in most states.



Effective analgesic activity within 30 minutes

Studies[6,7] show that effective analgesic results can be achieved with VICODIN within 30 minutes.



Long-lasting analgesic effects

The usual adult dose is one tablet every six hours, as needed.

Dosage is adjusted according to the severity of pain and the response of the patient.

Central and peripheral sites of action for greater pain relief

Hydrocodone in VICODIN™ alleviates pain through central effects while the acetaminophen in VICODIN works at the site of pain as well as on the CNS.

Thus, complementary analgesic effects are achieved with two drugs that work at two different sites.

Description: Each tablet of VICODIN contains:
Hydrocodone Bitartrate 5 mg.
(Warning: May be habit forming.)
Acetaminophen (APAP) 500 mg.

Acetaminophen occurs as a white, odorless crystalline powder, possessing a slightly bitter taste.

The hydrocodone component is dihydrocodeinone, a white, odorless crystalline powder which is derived from the opium alkaloid, thebaine.

Actions: The principal analgesic ingredient, hydrocodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; most of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the hydrocodone in this drug are analgesia and sedation.

Hydrocodone is similar to codeine and methadone in that it retains at least one half of its analgesic activity when administered orally.

This drug also contains the non-narcotic antipyretic-analgesic acetaminophen.

Indications: For the relief of moderate to moderately severe pain.

Contraindications: Hypersensitivity to hydrocodone or acetaminophen.

Warnings: Drug Dependence: Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, VICODIN (hydrocodone bitartrate with acetaminophen) is subject to the Federal Controlled Substances Act.

Usage in Ambulatory Patients: Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, VICODIN should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweight the possible hazards.

Usage in Children: VICODIN should not be administered to children.

Precautions: Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of VICODIN or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: VICODIN should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.

Adverse Reactions: The most frequently observed adverse reactions include light headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: The usual adult dose is one tablet every six hours as needed for pain. Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended above in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. VICODIN is given orally.

Drug Interactions: The CNS depressant effects of this drug may be additive with that of other CNS depressants. See **Warnings.**

Management of Overdosage: Signs and Symptoms: Serious overdose with VICODIN (hydrocodone bitartrate with acetaminophen) is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, criculatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of this drug may, in addition, result in acute hepatic toxicity.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Acetaminophen in massive overdosage may cause hepatotoxicity in some patients. Clinical and laboratory evidence of hepatotoxicity may be delayed for up to one week. Close clinical monitoring and serial hepatic enzyme determinations are therefore recommended.

Treatment of acute acetaminophen overdosage is purely symptomatic.

How Supplied: Available as white, bisected, flat capsule-shaped tablets with a double K logo.

- Bottles of 100. NDC #0044-0727-02.
- Hospital Unit – Dose dispenser (reverse numbered 25) available in 100's (4 x 25) pak NDC #0044-0727-01.

PRINTED IN U.S.A. AUGUST 1978

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Effect of Proximal Gastric Vagotomy on Feeding Stimulated Heidenhain Pouch Acid Secretion and Gastrin Release

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Truncal vagotomy (TV) is known to increase the feeding stimulated acid output of Heidenhain pouches. A series of experiments were performed in dogs to see if proximal gastric vagotomy (PGV) also had this effect. Dogs were prepared with gastric fistulas (GF) and Heidenhain pouches (HP). Gastric function testing included three categories of tests: (1) serum gastrin determinations and Heidenhain pouch acid secretion after feeding, (2) gastric emptying and simultaneous Heidenhain pouch acid secretion, and (3) gastric and Heidenhain pouch acid secretion and serum gastrin levels after insulin. Complete testing consisting of two control and two post-PGV tests was accomplished in five dogs in each category. Insulin testing confirmed that an adequate PGV was performed because GF peak acid output in response to 0.5 U/kg insulin IV was reduced 88% by PGV ($p < .01$). In response to two separate meals peak acid output (PAO) from the HP's was not increased significantly after PGV: Meal I pre-PGV 450 ± 112 vs post-PGV 400 ± 99 μEq/15 min; Meal II pre-PGV 256 ± 62 vs post-PGV 304 ± 150 μEq/15 min. This finding may represent an important physiologic difference between PGV and truncal vagotomy.

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PROXIMAL GASTRIC VAGOTOMY, also known as superselective vagotomy or highly selective vagotomy, is currently a contender for a position as an important operation for the reduction of gastric acidity in man.[5] Uncritical extrapolations of data obtained in the dog and applied to the human are dangerous because of known species differences. Nevertheless, because of the similarity of much of the gastric physiology of the two species and the impossibility of obtaining some of the data in man, we have investigated, in dogs, some of the alterations in gastric secretion that occur following PGV in the hope that a better understanding of the operation and its physiologic consequences might be attained. In dogs truncal vagotomy has been reported to sensitize Heidenhain pouches to feeding stimulation, so that the pouches secrete more acid after truncal vagotomy, than before.[7,10] This effect is also seen even if the stomach has been previously removed[8] or if only an extragastric vagotomy is performed.[9] The present study was undertaken to determine whether PGV increases Heidenhain pouch acid secretion in response to a meal. Concommitant with the feeding tests serum gastrin levels were measured in one series of experiments and gastric emptying was measured in another series of experiments to correlate these two factors with Heidenhain pouch acid secretion.

Methods

Surgical Procedures

Seven mongrel dogs weighing between 20–27 kg were each prepared with a Heidenhain pouch which had its blood supply from the vasa brevia. Each pouch was shown by biopsy to be free of antrum, and each was drained by a Gregory cannula. Pouch volume was from 75 to 125 cc. The main stomach was drained from a dependent point by a modified Thomas cannula.

Prevagotomy testing of the dogs was begun after a three week recovery period. Following these tests, proximal gastric vagotomy (PGV) was performed. The distal margin for the vagotomy was the double branched crow's foot configuration of the nerves of Latarjet which are located approximately 5 cm from the pylorus in dogs. Proximally, dissection was carried 5 cm up the esophagus into the mediastinum. All branches of the vagus nerves entering the distal 5 cm of the esophagus and the stomach down to the entry of the nerves of Latarjet were thereby divided, leaving the lesser curvature of the stomach bare. Arterial blood supply to the stomach from the right gastric artery and the right and

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Received: November 26, 1977.

0003-4932/78/1100/0647 $00.75 © J. B. Lippincott Company

left gastroepiploic artery remained intact. Care was taken to preserve both the anterior and posterior nerves of Latarjet, the hepatic branch of the anterior vagus nerve in the gastrohepatic ligament, and the celiac branches of the posterior vagus nerve going to the small bowel along the left gastric artery. Testing was then resumed after a three week recovery period.

Gastric Function Tests

Gastric function tests were performed no more often than twice a week and not on consecutive days. Food, but not water, was removed from the dogs' cages the afternoon prior to testing. The unsedated, alert dogs were tested while standing in Pavlov slings. Acid secretions were collected at 15 minute intervals and, using a pH meter-autoburette titration system (Radiometer, Copenhagen), acid concentration was determined by titration to pH7 with 0.2 N NaOH. Total acid output was determined by multiplying secretory volume times acid concentration. All tests were preceeded by at least one 15 minute basal collection period. Each kind of test was performed at least twice in each dog in the prevagotomy state and twice after PGV. Five dogs had complete testing in each category. The mean result of the prevagotomy tests was compared with the mean result of the post-PGV tests and the differences in the means were analyzed with Student's t test for paired values.

Serum gastrin levels and Heidenhain pouch acid secretion after feeding. The dogs were fed a half can of Ken L Ration® (Quaker Oats Co., Chicago, IL) (230 g) which they routinely ate in less than two minutes. Heidenhain pouch acid secretion was collected for four hours and acid output was determined. Venous blood samples were taken at 15, 30, 90 and 180 minutes and the serum analyzed for gastrin using the Squibb Radioimmunoassay Kit (E. R. Squibb & Sons, Inc., Princeton, NJ). Tests were run in duplicate and samples of known gastrin content were used in each test for quality control. The control and post-PGV samples for each dog were run in single assays.

Gastrin emptying and simultaneous Heidenhain pouch acid secretion. A gruel, the consistency of thick pea soup was made by combining 1000 cc of Respond 2000® dog biscuit (Agway Inc., Syracuse, NY) and 2000 cc of water, and allowing the mixture to sit overnight. Using a special adaptor on the Thomas cannula, 300 cc of this gruel was injected gently into each dog's stomach. At 30 minute intervals the material in the dog's stomach was allowed to drain out, was measured and then reinjected. The material emptied completely from the stomach within five minutes as confirmed by gentle digital examination of the stomach. When the residual was less than 25 cc, the stomach was considered empty. Heidenhain pouch acid secretion was measured at 30 minute intervals during these tests.

Acid secretion and serum gastrin levels after insulin. Regular insulin U-100 (Eli Lilly & Co., Indianapolis, IN) 0.5 U/kg was injected by intravenous bolus. The rate of acid secretion from the dog's gastric fistulas and Heidenhain pouches was determined for two hours. Serum gastrin was determined at 30, 60 and 90 minutes.

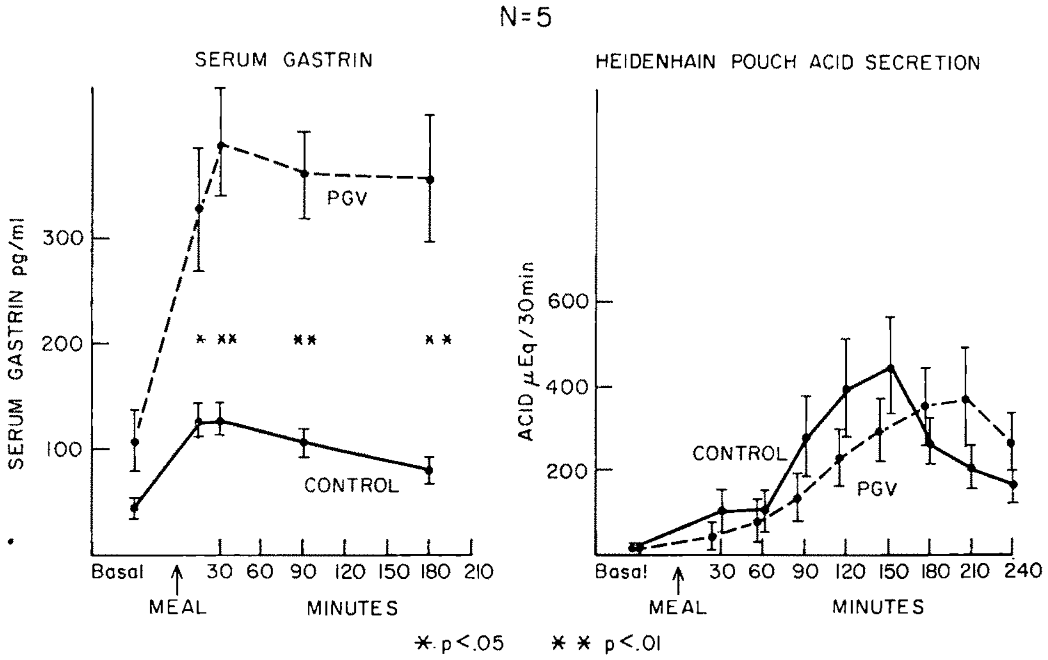

FIG. 1. Serum gastrin levels and Heidenhain pouch acid secretion rates in response to a Ken L Ration meal, done in the same five dogs before and after PGV. Serum gastrin levels increased while Heidenhain pouch acid secretion remained unchanged.

Results

Heidenhain Pouch Acid Secretion and Serum Gastrin Levels After Feeding (Fig. 1)

Heidenhain pouch acid secretion in response to a Ken L Ration meal was not increased after PGV. No significant change occurred in either peak acid output (450 ± 112 μEq/15 min before vs 400 ± 99 μEq/15 min after PGV) or in the total acid output in the 240 minutes following a meal. PGV did not significantly change basal serum gastrin levels. Postfeeding gastrin levels were increased after PGV at 15, 30, 90 and 180 minutes following feeding.

Gastric Emptying and Simultaneous Heidenhain Pouch Acid Secretion (Fig. 2)

Heidenhain pouch acid secretion in response to the gruel meal used for the gastric emptying tests was not changed by PGV in the four dogs tested with peak acid output being 256 ± 62 μEq/15 min before PGV and 304 ± 150 μEq/15 min after PGV. In two dogs peak acid output increased and in two others it decreased. Final gastric emptying was completed by 90 minutes in both the control and post-PGV tests. At 30 minutes after feeding, however, the residual volume in the control tests was 170 ± 12 ml compared with 125 ± 11 ml after PGV ($p < .05$). This is consistent with faster early emptying in the dogs after PGV The mean 60 minute gastric residuals were not significantly different.

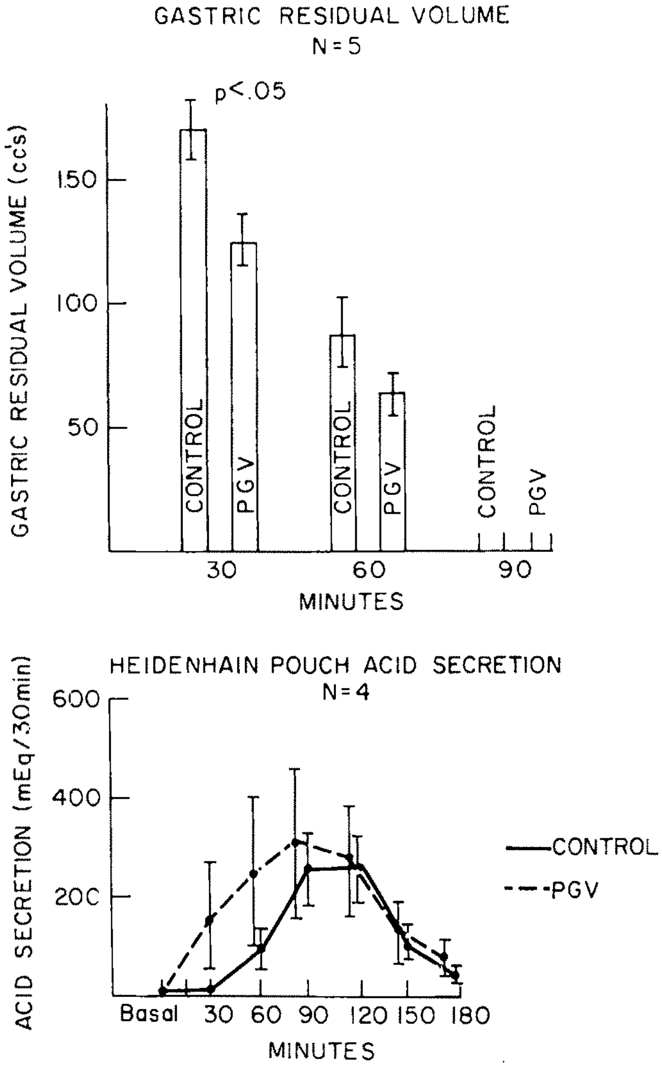

FIG. 2. Gastric emptying and simultaneously collected Heidenhain pouch acid secretion are shown for five dogs before and after PGV. Initial gastric emptying was faster after PGV than before. Heidenhain pouch acid secretion remained unchanged.

Acid Secretion and Serum Gastrin Levels After Insulin (Figs. 3 and 4)

Mean peak acid output (PAO) from the gastric fistulas in response to insulin was reduced by PGV from 3,059 ± 659 μEq/15 min to 362 ± 122 μEq/15 min ($p < .01$). The mean reduction was 88%. The reduction in insulin stimulated secretion in individual dogs ranged from 62% to 99%. The mean increase in gastric fistula acid concentration in response to insulin was 101 ± 6 mEq/L in the control tests compared with 64 ± 12 mEq/L in the post-PGV tests ($p < .05$).

Serum gastrin levels were not significantly increased by insulin in either the pre- or post-PGV tests. There was no Heidenhain pouch acid secretion in response to insulin after PGV or before.

Mean blood glucose levels before and 30 min after insulin were 82 ± 3 and 44 ± 3 mg/dl before PGV and 96 ± 4 and 53 ± 4 mg/dl after PGV.

Discussion

In these experiments, meal stimulated Heidenhain pouch acid secretion was not increased after PGV. No statistically significant change in acid secretion was evident whether the data were analyzed using sequential 30 minute acid output, or by integrated acid output. This observation is in marked contrast to the elevated Heidenhain pouch acid output in response to feeding seen after TV.[7–10] It also differs from the findings of a previous study of PGV.[1] In this earlier study by Amdrup, Heidenhain pouch acid secretion was collected in 24 hour samples before and after PGV. The results of this method usually parallel feeding response, but the 24 hour secretions collected by Amdrup differ from our feeding tests. It is noteworthy that two of the seven dogs tested in that study did not have elevated 24 hour acid output from their Heidenhain pouches showing that their results were not entirely uniform. In

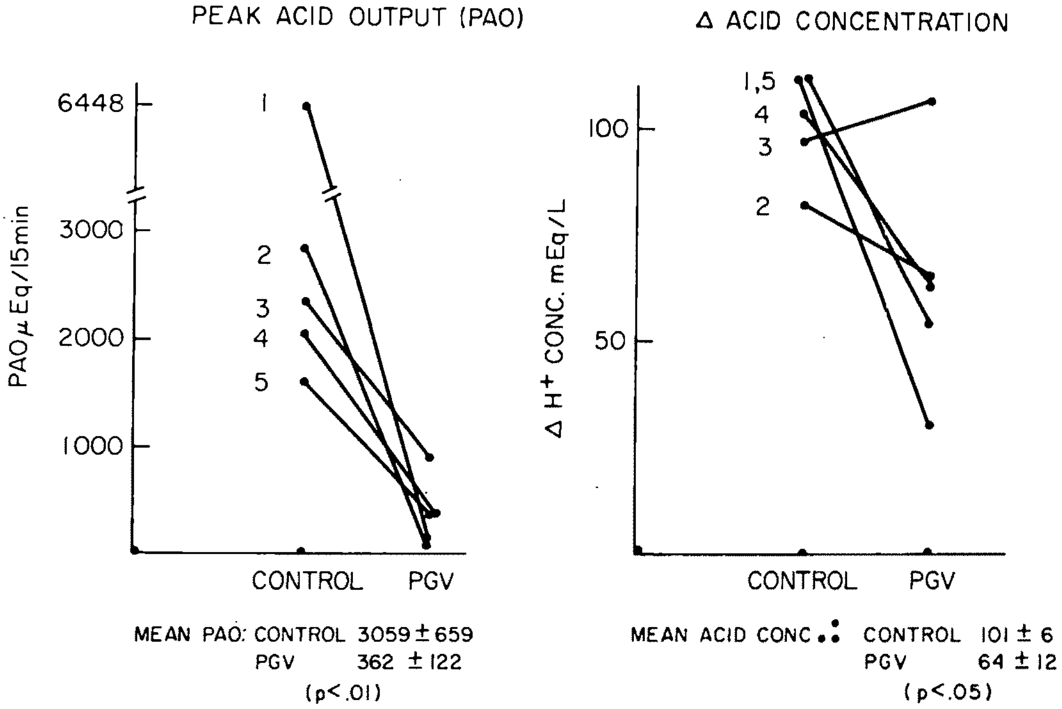

FIG. 3. PGV reduced insulin stimulated gastric fistula peak acid output by 88%.

our study the gastric emptying was tested and prompt emptying confirmed that each dog had preservation of antral innervation. This confirmation was lacking in Amdrup's study. If the antrum was denervated in some of her dogs this might explain an increased response in those dogs which would not be attributable to PGV.

The pattern of gastric emptying we observed after PGV differed from that observed prevagotomy, with faster early emptying and no delay in final emptying. This same pattern of emptying after PGV has been previously observed using isotope techniques.[3,11] After TV final emptying is greatly delayed.[3,11] Our method was useful for screening purposes to determine that each dog emptied without delay. The method is not satisfactory for making definitive statements about gastric emptying because it does not distinguish between the contribution of gastric secretion and gastric emptying in changing the observed residual volume.

The measurement of serum gastrin along with Heidenhain pouch acid secretion demonstrated a paradox. While postprandial Heidenhain pouch acid secretion was unchanged, postprandial serum gastrin levels were markedly increased. Similar increases in postprandial serum gastrin levels have also been seen after truncal vagotomy.[7] The paradoxical finding was that serum gastrin levels, but not Heidenhain pouch acid secretion rates, were elevated after PGV. This runs counter to the classic notion that Heidenhain pouch acid secretion is a biological assay of serum gastrin levels. Perhaps this paradox can be resolved by considering the percentage increases in serum gastrin. While the absolute levels of feeding stimulated serum gastrin were increased after

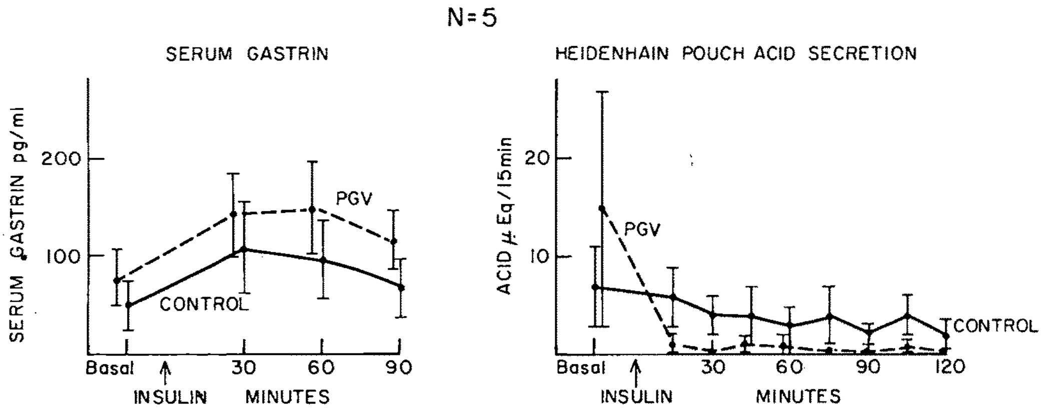

FIG. 4. Insulin failed to stimulate Heidenhain pouch acid secretion both before and after PGV. Serum gastrin levels were not increased by insulin either before or after PGV.

TABLE 1. *Serum Gastrin Levels in Response to Feeding (5 dogs)*

	Basal	30 min	60 min	90 min	180 min
Pre-PGV					
Gastrin pg/ml	46	127	128	107	80
% of basal	(100%)	(276%)	(278%)	(232%)	(173%)
Post-PGV					
Gastrin pg/ml	107	327	391	362	356
% of basal	(100%)	(306%)	(365%)	(338%)	(332%)

PGV, the percentage increases of basal serum gastrin following feeding were similar before and after PGV as shown in Table 1. The percentage increases from basal serum gastrins at 30, 60, 90 and 180 minutes after feeding before PGV were 276, 278, 232 and 173%. After PGV at the same intervals the per cent increases were 306, 365, 338 and 332. The per cent increases in serum gastrin levels were greater after PGV than before but the difference was not as marked as when the absolute values of serum gastrin were compared.

The measurement of insulin stimulated acid secretion and gastrin levels in our study indicated that PGV was being properly performed. Insulin stimulated acid secretion was reduced 88% in this study. This compares with an 85% reduction in 2-deoxyglucose stimulated acid secretion in dogs observed by Kaynan et al.[6] In both our study and the Kaynan study all dogs had an increase of 20 mEq/L or more in H^+ concentration in response to insulin (one criterion for a positive Hollander test)[4] after PGV despite the impressive reduction in acid secretion. Amdrup et al. also had similar increases in acid concentration in five of seven dogs after PGV.[1] This contrasts with the results of insulin stimulation tests after TV when a negative Hollander test is routinely observed along with a nearly 100% reduction in acid output.[2]

The Heidenhain pouch acid secretion and serum gastrin level studies after insulin answer a theoretical objection to PGV. Vagal release of gastrin is usually blocked by the simultaneously released acid from the fundus bathing the antrum. PGV might prevent fundic acid release and leave the antrum innervated but free of acid and thereby capable of releasing gastrin. This postulated outcome did not develop, however, as neither insulin stimulated serum gastrin levels nor acid secretion from the Heidenhain pouches were increased after PGV.

In conclusion these studies confirmed multiple previous reports that PGV without pyloroplasty can markedly reduce hypoglycemia stimulated gastric acid secretion while preserving near normal gastric emptying. Truncal vagotomy is known to increase postprandial Heidenhain pouch acid secretion in dogs.[7–10] This sensitization of Heidenhain pouches did not occur after PGV and may be an important physiologic difference between PGV and truncal vagotomy.

Acknowledgments

The authors are grateful for the technical assistance with the dogs of Sp5 John W. Carmer and Sp4 Clifford D. Lewis and for the assistance of James E. Rogers and the Nuclear Medicine Service, Walter Reed, with the gastrin radioimmunoassay.

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Pancreatic Pseudocyst—Operative Strategy

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The experience with 131 patients with 157 pseudocysts is reported. One hundred and twenty patients with 146 pseudocysts underwent 165 operations. There were ten operative deaths (8.3%) three of which were not attributable to the pseudocyst or its operative management. Sixteen patients died six months to 14 years after operation. Deaths in six of the 16 patients were in part attributable to pancreatitis or complications of pseudocyst management. The operative mortality was highest in patients undergoing incision and drainage and cystoduodenostomy. Other factors influencing mortality unfavorably included postoperative gastrointestinal hemorrhage from a pseudocyst; rupture or fistulization of the cyst into the gastrointestinal tract if associated with hemorrhage, and evidence of common duct obstruction, or the location of cysts in the head or uncinate process of the pancreas. Visceral angiography should be performed on all patients with pseudocysts. The risk of massive gastrointestinal or intra-abdominal hemorrhage is highest in the 10% of patients having pseudoaneurysms associated with their pseudocysts. Incision and drainage of pseudocysts is associated with a high rate of recurrence of the cyst and continued pain. Incision and drainage should only be used if the cyst is infected, or the cyst wall is not mature enough to hold sutures. Cystogastrostomy and cystojejunostomy are the procedures of choice for mature cysts. The presence of a pseudoaneurysm visualized on preoperative visceral angiography is an indication for an excisional operation as are the presence of multiple cysts, compression of the common duct or duodenum by the cyst, evidence of left sided portal hypertension, recurrent cysts or evidence of chronic pancreatitis.

RECENT REPORTS ON THE MANAGEMENT of pancreatic pseudocysts do not show results which should lead to complacency[20] by surgeons dealing with these patients. The operative mortality rate is in the range of 3–11%,[4,8,9,14,16,18,20,21] and postoperative complications develop frequently, 37%,[17] 34%[19] often requiring reoperation. Preoperative complications of pseudocysts afflict 30–55% of patients.[1,8,14] The recurrence rate, or persistence of unrecognized or de novo pseudocysts or ascites ranges from 11–20%[1,13,16] and pain due to chronic pancreatitis sufficient to require reoperation or rehospitalization occurs in up to 48%[8] of patients.

Authors in recent years have focused attention on some of the preoperative complications which effect 30–55% of patients with pseudocysts. The mortality and morbidity is the highest in patients with these preoperative complications. For example, in 1975 Sankaran and Walt[14] reported on their experience with 112 patients with pseudocysts, "Four of seven patients (57%) with preoperative bleeding and seven of eleven (64%) with postoperative bleeding died . . . ten of 14 patients in the entire series who died bleed either pre or postoperatively." The same authors reported pancreatic ascites in 14.5% of their patients. The recurrence rate of cysts was particularly high (40%) in patients with both a pseudocyst and ascites.

In Bradley and Clements 1976 report[3] on transenteric rupture of 37 pancreatic pseudocysts the incidence of this complication was estimated to involve 5% of all patients with pseudocysts. One third of their patients with transenteric rupture concomitantly developed massive hemorrhage. All patients with transenteric rupture who died (37%) died from hemorrhage.

Based on our experience at the University of Michigan we believe rational operative management of pseudocysts, particularly the choice of the appropriate operative procedure, depends particularly on a knowledge of preoperative complications, whether the cysts are multiple, recurrent or associated with chronic pancreatitis, the optimal time of operation, the size and location of the cyst, its adherence to surrounding structures and the disease initiating pancreatic inflammation.

Clinical Material

At the University of Michigan Medical Center and affiliated hospitals between the years 1959–1976 the diagnosis of pseudocyst of the pancreas was established in 131 patients. No operation was performed in 11 patients, four of whom died. Death was attributed to a ruptured pseudocyst in one of the four patients. The

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Submitted for publication: December 5, 1977.

0003-4932/78/1100/0652 $01.05 © J. B. Lippincott Company

presence of a pseudocyst was an incidental finding at autopsy in the other three patients. One hundred and 20 patients were subjected to operative intervention for 147 pseudocysts.

Of the 131 patients, 86 were male and 45 female. The average age at operation was 42 years and ranged from 8–83 years. Eighty-seven (66%) patients were alcoholic, four of whom also had gallstones. No known cause of pancreatic disease was identified in 19 patients. Eleven patients developed pseudocysts following trauma, one of whom was an alcoholic and another of whom had gallstones. Six patients had gallstones, five familial pancreatitis or congenital abnormalities of the pancreas and biliary tract, and three disorders of lipid metabolism.

Patient Presentation

Most patients with pseudocysts requiring operation other than those with trauma had had previous experience with pancreatitis. Seventy four per cent of patients had more than one episode of pancreatitis and 28% had had persistent pain for more than three months prior to operation. In only 2% of patients did the first episode of pancreatitis associated with pseudocyst result in operation. Twenty-four per cent of patients had had four previous hospitalizations for pancreatitis, 67% two to three hospitalizations and in only 9% was the first hospitalization associated with an operation. The history of an episode of pancreatitis or blunt abdominal trauma followed by persistence or recurrence of the signs and symptoms and clinical evidence of pancreatitis after 10–14 days including the appearance of an abdominal mass were features which often accompanied the development of a pseudocyst.

Symptoms and Signs

Most patients (91%) with pseudocysts had episodes of abdominal pain often with radiation to the back, 63% an abdominal mass and 21% were jaundiced. Less frequently noted were preoperative gastrointestinal hemorrhage 7.5%, pleural effusion 11%, fever 10%, and ascites 7%. In addition continuous or recurring episodes of pain, evidence of diabetes and calcification of the pancreas were considered suggestive of chronic pancreatitis.

Laboratory Data

At the time of the hospital admission associated with operative treatment of the pseudocyst the serum amylase levels were elevated in 77% of patients and the white count was elevated in 40% of patients. The hematocrit was below 38 in 17% of patients some of whom had bled into the G.I. tract. Conversely, the hematocrit was elevated above 50% in 6% of patients most of whom had been under replenished with fluids subsequent to an exacerbation of pancreatitis. Evidence of extra hepatic obstruction with elevation of alkaline phosphatase or bilirubin was noted in 21% of patients. Liver chemistries, SGOT, SGPT were abnormal in 10% of patients and visceral protein stores depleted in 12% evidenced by an albumin of under 3.5 g 100 ml. The serum calcium was depressed below 8.5 mg% in 12% of patients most of whom were admitted during an acute exacerbation of pancreatitis. One patient had an elevated serum Ca^{++} level and was subsequently found to have hyperparathyroidism.

Diagnostic Studies

Most of our patients were managed prior to the availability of endoscopy and ultrasound. Confirmation of the presence of a pseudocyst suspected on the basis of an abdominal mass detected on physical examination or suspected on the basis of the patient's clinical course was dependent on chest x-rays, flat plate, upright abdominal films and G.I. series 67%, and angiographic findings 28%.

Operative Findings

Thirty-eight per cent of the pseudocysts were located in the head or uncinate process and 37% in the body of the pancreas. Fourteen per cent of the pseudocysts were found in the tail of the pancreas and 3% of the cysts occupied parts of the head, body and tail. Four per cent of patients had cysts located in the small and large bowel mesentery which appeared unconnected to the pancreas. The incidence of multiple pseudocysts was 11%.

Size of Cyst

The cyst's size was estimated by the operating surgeon to exceed 10 cm in 30% of the patients.

Contents of Cyst

The cysts when opened or aspirated at operation were found to contain blood in 10% of patients, toothpaste like debris in 11%, or a liquid in 79% which was clear or straw colored in 88% and opaque or brownish red in 12%. In 18% of patients cyst fluid amylase levels were determined. These values ranged from 600 to over 5,000 somogyi units.

Other Findings

Ascitic fluid was found at operation in 7% of patients with pseudocysts. However, in only three patients was ascites a significant factor in the clinical course and

TABLE 1. *Initial Operative Treatment (Incision and Drainage, 34 Patients)*

No. Pts.	%	Status	Av. Years Follow-up
6	17.6	Alive, working, well	4.4
1	2.9	Alive, not working, well	6
1	2.9	Alive, not working, pain	3
1	2.9	Alive, working, pain	9
3	8.8	Lost to follow-up (3–alive, working, well)	4
17	50.	Failure–requiring reoperation because of recurrence of pain	
		Deaths	
4	11.8	Operative	
1	2.9	*Late*–not related to pancreatic disease	1
34	100	Total	
		Celiotomy	
9	100	Failure requiring reoperation	

operative indications. Six patients were noted on the basis of arteriography, operative or autopsy findings to have splenic vein thrombosis.

Operative Indications

Documentation of the presence of a pseudocyst after 10–21 days of symptoms by ultrasound, E.R.C.P., or radiographic techniques including angiography and gastrointestinal barium contrast studies was not necessarily an indication for operative intervention. For remission of symptoms and spontaneous resolution of the cyst may occur as happened with eight of our patients. Because of the possibility of spontaneous resolution of the cyst, operation was most often postponed until symptoms or findings of an abdominal mass persisted six weeks or more unless concern about the possibility of an abscess prompted earlier operative intervention.

Choice of the Initial Operation

Incision and Drainage—Table 1

Thirty-four patients at the time of initial operative intervention underwent incision and drainage of a pseudocyst. Most of these patients were operated on less than the usually recommended six weeks after the onset of symptoms from their most recent exacerbation of pancreatitis. Low grade fever, persistent ileus, weight loss, abdominal pain and tenderness and distension were sufficiently severe as to raise the spector of a pancreatic abscess or perforated ulcer. The decision to externally drain the pseudocyst encountered was sometimes inappropriately based on the elapsed time from the onset of symptoms of pancreatitis until operation rather than on the thickness of the cyst wall as visualized at operation.

Celiotomy—Table 1

Besides the 34 patients initially undergoing incision and drainage an additional nine patients underwent celiotomy to rule out a surgically correctable cause of their abdominal signs and symptoms such as perforated ulcer or acute cholecystitis, pseudocyst or intra-abdominal abscess.

Internal Decompression

Forty-two patients came to operation initially after a period of illness averaging six months (Tables 2–4). The decision to decompress the pseudocyst was based on the thickness of the cyst wall which could be verified at operation. The specific mode of decompression at operation was determined by the cysts location and whether it was adherent to the stomach or duodenum. In 17 of 24 patients undergoing cystogastrostomy the cyst was known to have been adherent to the posterior wall of the stomach at the time of operation. Cysts not in close proximity to the stomach or duodenum were treated by Roux-en-Y cystojejunostomy in 13 patients. The Roux-en-Y limb was 18–24 cm in length.

Excisional Operations—Table 5

Excisional operations, proximal or distal, were initially utilized in the management of 31 patients with pseudocysts principally because of preoperative complications or evidence of pre-existing chronic pancreatitis. Preoperative complications necessitating or making more desirable an excisional operation consisted of gastrointestinal hemorrhage from pseudoaneurysms of the mesenteric vessels in four patients, common duct obstruction in four patients and multiple cysts in five patients. Technical inability to drain a cyst in the

TABLE 2. *Initial Operative Treatment (Cystogastrostomy, 24 Patients)*

No. Pts.	%	Status	Av. Years Follow-up
7	29.2	Alive, working, well	3.3
2	8.3	Alive, not working, well	2
1	4.2	Alive, not working, pain	1
4	16.6	Lost to follow-up	
		(3–alive working well)	1
		(1–alive not working pain)	2
9	37.5	Failure–requiring reoperation because of recurrence of pain	
		Death	
1	4.2	In part due to pancreatitis	2 months
24	100	Total	

uncinate process necessitated excision of the pseudocyst in three patients as did duodenal obstruction in two patients.

Proximal resection of the pancreas was performed in five patients and distal resection in 26. Fifteen of the 31 patients with pseudocysts who underwent an excisional operation had no preoperative complications other than evidence of chronic pancreatitis. In eight patients an excisional operation was performed to relieve pain. Sometimes only late in the dissection in an enlarged indurated inflamed gland was a cyst noted to be present. Pancreatectomy was deemed the operation of choice by the operating surgeon in the other seven patients with pseudocysts.

Results

The results of the initial operative intervention are reported by operations in Tables 1–5 and summarized in Table 6. Information about the patient's status on follow-up was obtained through a hospital visit, or from the patient by phone call or written questionnaire or the patient's physician.

Patients were considered to be well if they remained free of pain, recurrent bouts of pancreatitis or a recurrence of their pseudocyst. Some patients survived the operative management of their pseudocysts and were free of pain but did not return to work usually as a result of malnutrition, alcoholism, or diabetes. These patients along with those who continued to have the pain of chronic pancreatitis were classified as doing poorly. Other patients were doing well at their last follow-up or until death from a cause unrelated to pancreatitis.

Reoperation Due to Persistent, Recurrent or New Cyst Formation or Chronic Pancreatitis

Forty patients required a second operation and five patients had a third operation. Of those 40 patients undergoing a second operation, 26 had recurrent, persistent or new cysts. Eleven patients were operated on because of pain. Of the five patients requiring a third operation, four were operated on for pain associated with chronic pancreatitis and one for either a persistent, recurrent or new cyst. The necessity of a second and sometimes a third operation was most likely to be required after celiotomy or incision and drainage.

TABLE 3. *Initial Operative Treatment (Cystojejunostomy, 13 Patients)*

No. Pts.	%	Status	Av. Years Follow-up
7	53.8	Alive, working, well	4.7
3	23.1	Lost to follow-up	
		2 alive, working, well	2.0
		1 alive, not working, well	4.0
3	23.1	Failure requiring reoperation	
13	100	Total	

TABLE 4. *Initial Operative Treatment (Cystoduodenostomy, 5 Patients)*

No. Pts.	%	Status	Av. Years Follow-up
1	20	Alive, working, well	9
1	20	Lost to follow-up	
		1 alive, working, well	1
1	20	Failure requiring reoperation	
		Death	
2	40	Operative	
5	100	Total	

The operative solution most frequently resorted to at reoperation was excision of the cyst (25 patients), cystojejunostomies (eight patients), and cystogastrostomies (six patients). These were the same operations which provided the most success following the initial operative procedure. The results of all the original operations plus reoperations are shown in Table 7.

Of the 56 excisional operations, five were pancreaticoduodenectomies, one a total pancreatectomy, 20 (80–95%) distal pancreatectomies and 28 (40–80%) distal pancreatectomies.

Exocrine and Endocrine Insufficiency

Diabetes was a sequela of 80–95% distal pancreatectomy about three times as often as after 40–80% distal resection or pancreaticoduodenectomy (Table 8). Clinically troublesome steatorrhea was most frequent after pancreaticoduodenectomy. The combination of a partial pancreatectomy and hemigastrectomy was most likely to produce steatorrhea. Patients having 80–95%

TABLE 5. *Initial Operative Treatment (Excisional Therapy, 31 Patients)*

No. Pts.	%	Status	Av. Years Follow-up
13	42.0	Alive, working, well	3
2	6.4	Alive, not working, well	3
2	6.4	Alive, not working, pain	4.5
1	3.2	Alive, working, pain	1.0
4	13.0	Lost to follow-up	
		3 alive, working, well	2.5
		1 alive, not working, well	2.0
5	16.2	Failure requiring reoperation	
		Death	
2	6.4	Operative	
		Late	
2	6.4	Not due to pancreatitis	
31	100	Total	

TABLE 6.

Status	I&D No.	I&D %	Celiotomy No.	Celiotomy %	Cystgast No.	Cystgast %	Cystjej No.	Cystjej %	Cystduod No.	Cystduod %	Excision No.	Excision %	Misc. No.	Misc. %
Failure														
Requiring reoperation	17	50.9	9	100	9	37.5	3	23.1	1	20	5	16.2	3	75
Deaths														
Operative	4	11.76							2	40	2	6.4		
Late														
Due to pancreatitis	1	2.94			1	4.2								
Not due to pancreatitis											2	6.4		
Alive & well	6	17.64			7	29.2	7	53.8	1	20	13	42.0	1	25
Alive, not working, well	1	2.94			2	8.3					2	6.4		
Alive, not working, pain	1	2.94			1	4.2					2	6.4		
Alive, working, pain	1	2.94									1	3.2		
Lost to follow-up														
Alive, well, working	3	8.82			3	12.4	2	15.4	1	20	3	9.75		
Alive, working, pain					1	4.2	1	7.7			1	3.20		
Total	34	100	9	100	24	100	13	100	5	100	31	100	4	100

resections were more prone to have trouble attaining their preoperative weight.

Postoperative Complications

Postoperative complications and morbidity after the initial operative procedure requiring reoperation affected 18 patients (15%) (Table 9). Hemorrhage from the cyst and G.I. tract were most frequently noted after incision and drainage, cystogastrostomies and cystojejunostomies. Intra-abdominal abscesses were most common following excisional operations. Peritonitis and hemorrhage resulted after a breakdown of the cystoduodenotomy anastomosis in two patients. The cyst and duodenum had been unfused in both patients (Table 4).

Among the 40 patients undergoing a second operative procedure to relieve the pain of chronic pancreatitis or a recurrent, persistent or new pseudocyst 15 (37%) developed complications. Abscesses occurred in 13 patients, eight after an excisional operation. Short lived episodes of pancreatic drainage were frequent from the distal pancreatic stump. Most of these fistulas were short lived and required no reoperation.

TABLE 7.

	Initial Operation 120 Patients	Reoperation 40 Patients	Total 120 Patients
I & D	34	4	38
Celiotomy	9		9
Cystogastrostomy	24	5	29
Cystojejunostomy	13	8	21
Cystoduodenostomy	5	2	57*
Excision	31	26	4
Miscellaneous	4	0	4
Operations	120	45	165

* Pancreaticoduodenectomy (5); total pancreatectomy (1); 80–95% distal pancreatectomy (21); 40–80% distal pancreatectomy (30).

Postoperative Gastrointestinal Hemorrhage

Ten patients developed massive gastrointestinal hemorrhage or intra-abdominal hemorrhage following operative decompression of their pseudocyst (Table 10). Five of the patients died without leaving the hospital, a sixth patient died shortly after discharge from a cerebral vascular accident.

Of the five patients who died in the hospital three bled into the gastrointestinal tract and two intra-abdominally. The source of hemorrhage was not identified in the two patients, one of whom had a cystoduodenotomy and the other a cystogastrostomy. A patient treated with external drainage bled from a pseudoaneurysm of the inferior pancreaticoduodenal artery. The two patients who bled after distal pancreatectomy had multiple pseudocysts. The source of hemorrhage was from unresected cysts in the head of the pancreas. Neither was subjected to arteriography. Pseudoaneurysms were associated with the inferior pancreaticoduodenal artery in one patient and the gastroduodenal artery in the other.

Of the four survivors, two bled into the G.I. tract and two intra-abdominally. Cystoduodenotomy and cystogastrostomy in one patient each and an excisional operation in two patients were associated with hemorrhage. Bleeding was controlled by arterial ligation in two patients. Hemorrhage ceased spontaneously in two patients. The patient who died from a cerebrovascular accident three months after cystogastrostomy bled from the G.I. tract. Hemorrhage was controlled by arterial ligation.

Those most at risk from the complications associated with pseudocysts were patients with hemorrhage occurring postoperatively and in whom bleeding originated from the inferior pancreaticoduodenal or gastroduodenal artery. Patients with multiple cysts, particu-

TABLE 8. *Incidence & Severity of Diabetes Pre & Postoperatively*

No. Pts.*	Operative Procedure	Diet & Oral		Insulin		Overall	
		Pre	Post	Pre	Post	Pre	Post
20	Incision & drainage	4	4	0	1	4 20%	5 25%
19	Cystogastrostomy	2	3	—	—	2 10.5%	3 15%
20	Cystojejunostomy	2	5	1	2	3 15%	7 35%
6	Cystoduodenostomy	1	2	—	—	1 16.6%	2 33%
28	40–80% pancreatectomy distal	3	4	1	5	4 14.2%	9 32%
19	80–95% pancreatectomy distal	5	2	—	15	5 25%	17 89%
5	Panc. duodenectomy	1	1	—	—	1 20%	1 20%
1	Total	1	0	0	1	1 100%	1 100%
118		19	21	2	24	21	45

* Number in whom information was available.

larly those located in the head of the pancreas complicated by bleeding or common duct obstruction were also a high risk group.

Rupture of the Pseudocyst

Rupture of the pseudocyst into the peritoneal cavity was a rare event in our experience though it resulted in the death of the only patient in whom it occurred.

More commonly noted were rupture or fistulization of cysts into the gastrointestinal tract (seven patients). In three patients rupture occurred into stomach or duodenum. Two of these three patients died from hemorrhage associated with a pseudoaneurysm in the cyst wall. Rupture occurred into the colon of two patients both of whom survived. Another patient survived rupture into the small bowel and another survived rupture into the chest.

Preoperative Complications of Pseudocyst

In ten patients with pseudocysts, hemorrhage was the presenting symptom (Table 11). Two bled intra-abdominally and seven into the G.I. tract. One person bled both intra-abdominally and into the gastrointestinal tract. Hemorrhage entered the gastrointestinal tract presumably through the pancreatic ductal system in continuity with the pseudocyst, or as occurs more frequently, by fistulization or erosion of the pseudocyst into the stomach or duodenum. The source of hemorrhage was a pseudoaneurysm of the splenic artery in six patients. The inferior pancreaticoduodenal artery two patients and the right gastroepiploic artery in one patient. The source of hemorrhage was unknown in one patient. Hemorrhage was controlled by an excisional operation in five patients, *i.e.*, one pancreaticoduodenectomy and four distal pancreatectomies. Ligation of the bleeding site was employed successfully in two patients, cystogastrectomy in a second and cystojejunostomy dismantling in a third. All ten patients with preoperative hemorrhage survived.

Common Duct Obstruction

Twenty patients with pseudocysts were hospitalized with jaundice secondary to common duct obstruction. Obstruction resulted from compression of the distal common bile duct by the cyst.

Five of the 20 patients whose common duct obstruction resulted from pseudocysts died. However, three of the five who died also had had postoperative hemorrhage. A sixth patient with common duct obstruction died later after leaving the hospital. Death was in part attributable to sequelae of his pseudocyst and pancreatitis.

Five surviving patients underwent excisional operation. Pancreaticoduodenectomy was performed in three patients because of multiple cysts or cysts in the uncinate process in which decompression was technically impossible, or because of a pseudoaneurysm associated with the cyst. Two patients undergoing

TABLE 9. *Complications Requiring Operative Intervention*

	Initial Operation 120 Patients 120 Operations No. Patients	*Reoperation* 40 Patients 45 Operations No. Patients
Hemorrhage	6	1
Peritonitis + hemorrhage	2	0
Abscesses	6	12
Common duct stricture	2	0
Small bowel obstruction	1	0
Colonic necrosis	1	0
Common duct stricture plus hemorrhage	0	1
Colonic fistula and abscess	0	1
	18 (15%)	15 (37%)

TABLE 10. *Hemorrhage (10 Patients Postoperative)*

	Original Operation	Hemorrhage	Autopsy	Vessel	Treatment	Outcome
H.	External drainage	Intraabdominal	Pseudo-aneurysm	Inf. panc. Duod.	Art. ligat.	Op death
L.	Distal panc & I&D abscess for pseudocyst	Gastrointestinal	Pseudo-aneurysm	Inf. panc. Duod.	Art. ligat.	Op death
R.	Cystoduodenostomy	Intraabdominal	?	Coagulopathy No operation		Op death
G.	Choledochojejunostomy	Gastrointestinal	Pseudo-aneurysm	Gastro-duodenal	Art. ligat.	Op death
F.	Cystogastrostomy	Gastrointestinal	?	?	No operation	Op death
Mc	Cystogastrostomy	Gastrointestinal	?	?	Art. ligat.	Late death C.V.A.
G.	Cystoduodenostomy	Gastrointestinal	No pseudo-aneurysm	?	No operation	S*
M.	Cystogastrostomy	Intraabdominal	Pseudo-aneurysm	Splenic	Art. ligat.	S
A.	50% distal panc.	Gastrointestinal	?	?	Ceased spontaneously 2 mo. later Cysto-jejunostomy	S
J.	80%—Cyst in head unroofed	Intraabdominal	No pseudo-aneurysm	?	No operation	S

* S—Survival.

distal resection for common duct obstruction also had a history of chronic pancreatitis.

Operative Deaths

There were ten operative deaths (8.33%) among the 120 patients in whom the pseudocyst was treated surgically (Table 12).

Three patients developed cysts within three to six weeks of an episode of hemorrhagic necrosis of the pancreas. The cysts developed in the head of the pancreas in two patients and produced common duct obstruction in one patient, and duodenal obstruction as well as common duct obstruction in the other. These three patients died more from hemorrhagic necrosis of the pancreas than from complications of the pseudocyst or its operative management (Table 12).

A patient with cirrhosis and portal hypertension died at the time of attempted 95% pancreatectomy. His problems could have been better managed by porta caval shunt and pancreaticoduodenectomy.

Three patients died from complications attributable to operative technique and judgment. Dehiscence of an anastomosis not in an area of fusion resulted in lateral duodenal fistulas and peritonitis in two patients. In the third patient, wound dehiscence peritonitis and sepsis was followed by a lethal gastrointestinal hemorrhage.

Three patients died as a result of massive postoperative gastrointestinal hemorrhage from a pseudoaneurysm in the cyst wall. The preoperative and operative

TABLE 11. *Preoperative Hemorrhage in Ten Patients*

	Hemorrhage	Autopsy or Angiography Findings	Artery	Treatment	Outcome
D.	Intra-abdominal	?	?	Cystogastrostomy	S*
B.	Gastrointestinal	Pseudoaneurysm	Splenic	Artery ligation	S
C.	Gastrointestinal	Pseudoaneurysm	Splenic	Cystogastrostomy & artery ligation	S
Mc	Gastrointestinal	Pseudoaneurysm	Inf. panc. Duod.	Cystojejunostomy	S
H.	Gastrointestinal	Pseudoaneurysm	R. Gastric	Cystojejunostomy dismantling	S
J.	Gastrointestinal Intra-abdominal	Pseudoaneurysm	Splenic	Distal resection	S
B.	Gastrointestinal	Pseudoaneurysm	Splenic	Distal resection	S
L.	Gastrointestinal	Pseudoaneurysm	Inf. panc. Duod.	Pancreaticoduodenostomy	S
A.	Gastrointestinal	Pseudoaneurysm	Splenic	Distal resection	S
T.	Intra-abdominal	Pseudoaneurysm	Splenic	Distal resection	S

* S—Survival.

TABLE 12. *Operative Deaths: Ten (8.3%)*

Patient Age	Sex	Preoperative Complication	Operation Pseudocyst	Postoperative Complication	Autopsy
41	F	Hemorrhagic pancreatitis, shock, renal & pulmonary failure	I & D		Hemorrhagic ascites necrotizing pancreatitis
42	M	Hemorrhagic pancreatitis shock, renal & pulmonary failure	I & D		Ascites, pleural effusion necrotizing pancreatitis, undrained cyst
59	F	Hemorrhagic pancreatitis renal & pulmonary failure, jaundice	I & D		Ascites, bilateral pleural effusion, common duct & duodenum obstructed by an unrecognized pseudocyst in the head of the pancreas
52	M	Cirrhosis and portal hypertension	95%	Operative hemorrhage	
47	F		Cystoduodenostomy	Anastomatic dehiscence	G.I. hemorrhage, peritonitis
51	M		Cystoduodenostomy	Anastomatic dehiscence	Peritonitis
47	M	Celiotomy wound dehiscence	Cystogastrostomy	Sepsis	G.I. hemorrhage
32	M		I & D	Hemorrhage	Pseudoaneurysm
45	M		Distal pancreatectomy for infected pseudocyst	I & D subhepatic abscess G.I. hemorrhage	Pseudoaneurysm
38	M	I & D ×2 50% distal	Multiple	G.I. hemorrhage	Pseudoaneurysm

diagnosis of pseudoaneurysm was not suspected. None of the patients had undergone selective preoperative angiography. None of the pseudocysts were excised as we recommend when associated with a pseudoaneurysm.

Late Deaths

There were 16 late deaths from operative decompression or excision of a pseudocyst.

Symptomatic Group

In six patients it was felt the patient's operation or persisting pancreatitis contributed in part to the patient's death (Table 13).

Symptom Free Group

Ten patients died from 1–11 years after operative decompression or excision of a pseudocyst. All were symptom free from problems unrelated to the operation on the cyst, alcoholism or pancreatectomy (Table 14).

Comments

The age of the cyst is an important factor influencing the timing of operation. However, it is sometimes impossible to be certain of the age of the cyst in patients with alcoholic pancreatitis having frequent exacerbations of their disease. The presence of the cyst may have antedated the most recent episode of pancreatitis which brought the patient under medical care. Unless there is convincing evidence of a pancreatic abscess characterized by a septic febrile course or some complication of a pseudocyst patients should not be subjected to operations in under six to eight weeks from the onset of the exacerbation of pancreatitis for several reasons. 1) In a very significant number of instances the acute cyst associated with an episode of pancreatitis demonstrated on ultrasound or visualized on E.R.C.P. will spontaneously resolve making the operation unnecessary. The exact incidence of spontaneous resolution is unknown but far higher than our reported 6% which preceded the use of ultrasound and E.R.C.P. Czaza[5] reported 70% of acute cysts resolve without operative

TABLE 13. *Late Deaths Symptomatic Group (Six Patients)*

Age	Operation	Cause of Death	Interval Operation to Death–Years
39 M	Celiotomy, 95% distal resection	Malnutrition, alcoholism	3
44 M	Cystjejunostomy, 85% distal resection	Alcoholism, exsanguination during porta caval shunt	2
49 M	Celiotomy, 50% distal resection and common duct exploration	Alcoholism, drug overdose	7
35 F	50% distal resection	Pain and alcoholism, died laminectomy	11
39 F	Cystgastrectomy	Pain, CVA	3 months
35 M	Cystgastrostomy, cystjejunostomy	Alcoholic hepatitis	2

TABLE 14. *Late Deaths Symptom Free Group (Ten Patients)*

No. Pts.	Cause of Death	Interval Operation to Death Years
3	Cerebral vascular accident	2, 4, 5
1	Intestinal obstruction	2
1	Peritonitis post D & C	2
1	Pneumonia	5
1	Pulmonary embolus	1
2	Myocardial infarction	1
1	Pulmonary emphysema	3

therapy. 2) Operative management of an acute cyst precludes the use of internal decompression the procedure of choice if the cyst wall is not sufficiently thick and mature to hold sutures. In experimental animals, according to Warren's[22] work, it required four to six weeks for a cyst wall to mature. This assumption has been challenged by Grace and Jordan,[6] based on their experience with a patient found to have a mature cyst who at an operation three weeks earlier had no cyst. However, most cysts require a longer period of maturation before their walls lend themselves to suturing. Sankaran and Walt[14] described four patients operated on less than four weeks after an acute attack three of whom had cysts which were thin walled and incompatible for internal drainage.

We support the opinion expressed by Grace and Jordan[8] that should one encounter at emergency operation a pseudocyst two to three weeks after an exacerbation of pancreatitis in which the wall is thick, the maturation of the wall and its ability to hold sutures should be the criteria as to whether internal decompression is feasible not the time interval from the acute exacerbation to operation.

3) When the cyst wall is too immature to hold sutures, external drainage in spite of its limitations must be employed. External drainage is associated with a high rate of complications or death in 60–80% of patients. This high morbidity and mortality may more often reflect the severity of the complications encountered and cannot always be attributed to the operation.[4] However, external drainage in our experience is not a definitive operation in the patient with either an acute or mature pseudocyst in over half the instances in which it is employed due to the high incidence of recurrent cysts and persistent symptoms necessitating reoperation. This has also been the experience of Scharplatz.[17]

Some unnecessary operations in the form of external drainage have been performed because the cyst fluid visualized at operation resembled the contents of an abscess. In order to avoid an unnecessary external drainage procedure the contents of the cyst at operation should be smeared and gram stained.

When a cyst is known to have been present for a period of six weeks prompt operative intervention is indicated. The only non-operative death occurred in a patient whose cyst of long standing ruptured. Evidence of expansion of an existing cyst is an indication for prompt operative intervention. Spontaneous hemorrhage and rupture are the most frequent causes of non-operative deaths.[1,19]

We recommend selective angiography of the superior mesenteric and coeliac arteries as part of the preoperative evaluation of all patients with pseudocysts. Pseudoaneurysms were identified in 13 (10.8%) of our operative cases. Hemorrhage is a significant factor in the majority of deaths of patients with pseudocysts.[1,3,9,14,16,19] We feel preoperative arteriography is an essential step in the selection of the most appropriate operation to avoid this preventable complication. All pseudocysts having an associated pseudoaneurysm should, whenever possible, be treated by excision. Preoperative or postoperative persistent massive hemorrhage from the pseudocyst did not occur in the absence of a pseudoaneurysm in any of our 13 patients evaluated by arteriography. In the absence of arteriography the source of hemorrhage was not known in seven instances. Failure to establish the presence of a pseudoaneurysm in conjunction with a pseudocyst may contribute to a fatal outcome (Table 12). At operation three of our patients, none of whom had bled preoperatively or had evidence of blood in their cysts at operation, underwent external drainage or internal decompression. Postoperatively all three exsanguinated. Pseudoaneurysms in the cyst wall were the source of hemorrhage. Preoperative angiography and an excisional operation would have eliminated the pseudoaneurysm and the possibility of postoperative hemorrhage from it. We had no mortality and successfully terminated the hemorrhage in all five patients treated by excisional operations. In contrast two of four of our patients treated by non-operative methods died and four of nine patients treated by local ligation of vessels died. Local control or ligation of the feeding vessel of a pseudoaneurysm embedded in a chronically inflamed pseudocyst wall is not always effective or technically feasible and the result is a 28% mortality from infection and rebleeding according to Stanley et al.[18] The success of excisional operations in reducing mortality of hemorrhage associated with pseudocysts pertains whether the hemorrhage originates from vessels in the head or tail of the gland. In our experience and that of others pancreaticoduodenectomy and distal pancreatectomy are equally effective and technically feasible in the treatment of the patient with a pseudocyst complicated by a pseudoaneurysm in the wall of the cyst.[18] In those patients thought too ill to withstand operative intervention intra-arterial embolization with gelfoam or autologous clot should be considered as a temporizing procedure.

Grace[8] reported the presence of blood or even active bleeding found at the time of operation as determined by needle aspiration of the pseudocyst did not expose the patient to any special risk of postoperative bleeding. We had the same experience in six patients but feel such a course is rational only if preoperative angiography has eliminated the possibility of an associated pseudoaneurysm. This distinction is crucial. In the absence of an associated pseudoaneurysm we do not feel it necessary to proceed with an excisional operation in cysts containing blood.

Internal decompression of the uncomplicated mature single pseudocyst by cystogastrostomy or cystojejunostomy are the procedures of choice (Tables 1–6). We recommend cystogastrostomy when the anastomosis can be performed through an area of fusion between the cyst and the posterior wall of the stomach. We employ a 10 cm long incision including a small ellipse of cyst wall. This ellipse of cyst wall is sent as a biopsy to rule out cystadenocarcinoma. While there is debate as to the appropriate size of the cystogastrostomy anastomosis, we were unable to demonstrate any difference in the rate of recurrence when a smaller anastomosis of 5–7 cm without an ellipse was employed. Hemorrhage from the edge of the anastomosis, as was reported by Huston[11] and Folk,[6] has not been a problem in our experience or that of Van Heerden.[20] We place multiple mattress sutures of permanent material circumferentially around the anastomosis in the area of fusion.

When the pseudocyst is not fused to the posterior wall of the stomach we believe a Roux-en-Y cystojejunostomy is the procedure of choice. The consequences of a dehiscence of a long Roux-en-Y cystojejunostomy are less catastrophic than a breakdown of an unfused cystogastrostomy or cystoduodenostomy. Warshaw[23] recommends the limb of the cystojejunostomy be at least 35 cm long presumably to alleviate the consequences of a dehiscence. We did not find any correlation between cyst recurrence and the length of the cystojejunostomy limb.

Sankaran[14] reported good results with cystoduodenostomy as did Mercadier[12] though the latter patients according to Scharplatz and White[17] were apparently not followed beyond nine months. We do not recommend cystoduodenostomy on the basis of our limited but unsatisfactory experience which included two deaths (Table 4) and one recurrence with this operation. Both deaths occurred in patients in whom the duodenum was not fused to the cyst as is recommended. Failure to follow accepted practice perhaps explains the events which led to dehiscence of the cystoduodenostomy anastomosis. However, Scharplatz[17] and also Grace[8] reported dissatisfaction with the long-term results of cystoduodenostomy.

Indications for an excisional operation in addition to a pseudoaneurysm associated with the pseudocyst includes patients having multiple pseudocysts, or cysts located in the uncinate process or head of the pancreas in which internal decompression is not technically feasible. Common duct or duodenal obstruction frequently cannot be relieved except by a pancreaticoduodenectomy due to the presence of one or more small cysts which do not lend themselves to internal drainage. Yet a small cyst or cysts in the head of the pancreas may initiate and perpetuate pancreatic inflammation and as Sankaran[14] and Nardi[13] have noted can produce very troublesome persistent symptoms. Sometimes these small cysts are not appreciated on E.R.C.P. and are impossible to identify by palpation at operation and are only recognized after pancreaticoduodenectomy is well under way.

Left sided portal hypertension from splenic vein thrombosis due to pericystic inflammation and compression by the cyst is best treated by distal pancreatectomy and splenectomy which relieves both symptoms of the cyst and left sided portal hypertension.[15]

Rupture or enteric fistulization of the pseudocyst in our experience was more common (six patients) than free intra-abdominal perforation (one patient), or extension into the chest (one patient). Enteric fistulization in itself was a benign process unless accompanied by hemorrhage secondary to pseudoaneurysm formation. The combination is lethal.[1,2,3,14,19]

Twenty-six of our patients have undergone operative decompression of a pseudocyst and subsequently required another operation for a pseudocyst. At the second operation it is often impossible to know if the cyst is new, recurrent, persistent, or overlooked at the first operation. For patients continuing to experience pain after internal decompression or an excisional operation (Table 7), the choice of which excisional operation proximal or distal pancreatectomy is most appropriate for the patient depends on whether the cyst, ductal obstruction or inflammation of the pancreas are confined to the head or tail of the pancreas.

Pancreatic Function

Distal resection of 80% or more of the pancreas is likely to cause insulin dependent diabetes in 79% of patients (Table 7). Pancreaticoduodenectomy preserves more endocrine function than distal pancreatectomy due to the retention of a greater mass of tissue in the tail of the pancreas which has a higher concentration of islets than the head or body.[7]

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Announcement

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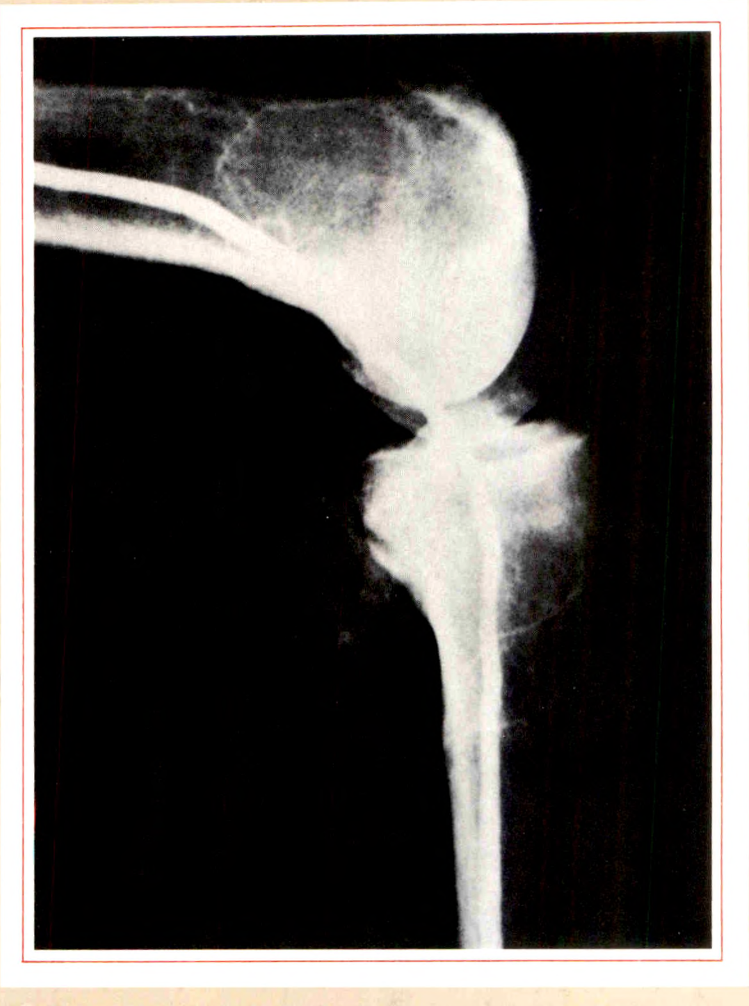
GORE-TEX® reinforced vascular grafts, after 60,000 implants:



What we've learned.

Summary of Clinical Data, as of September 25, 1978.

Operation type	Number Implanted	Number Patent	% Patency	Avg. Months Weighted Experience	Months Maximum Experience
Above-Knee					
Fem-pop	1740	1526	88%	3.6	34
Ilio-fem	153	145	95%	4.1	22
Ilio-pop	58	54	93%	2.1	18
Fem-fem	105	98	93%	2.3	20
Pop-segmtl	14	11	79%	1.3	17
Aorta-pop	21	16	76%	2.4	14
Aorta-fem	133	128	96%	6.4	29
Axil-fem	143	132	92%	1.7	14
Axil-bifem	31	31	100%	3.7	16
Aorto-iliac	5	5	100%	2.0	6
Fem-profunda	14	11	79%	1.9	15
Axil-pop	19	17	89%	5.5	16
Iliac-fem	2	1	50%	3.5	7
Iliac-pop	10	7	70%	6.0	24
Others	4	2	50%	<0.5	1
Group Totals	2452	2184	89%	3.6	34
Below-Knee					
Fem-dist-pop	958	792	83%	3.2	34
Fem-ant-tibial	183	129	70%	1.5	19
Fem-post-tibial	292	197	67%	2.6	38
Fem-peroneal	111	78	70%	1.7	22
Aorta-ant-tib	2	1	50%	0.0	0
Ileo-post-tib	5	4	80%	1.2	6
Ileo-pop	5	3	60%	3.0	5
Fem-dorsalis ped	24	13	54%	3.0	12
Aorto-dist pop	5	5	100%	4.8	7
Iliac ant-tib	4	4	100%	3.2	8
Axil-dist-pop	2	2	100%	11.0	13
Iliac-dist-pop	4	2	50%	0.5	1
Pop-post-tib	2	2	100%	0.5	1
Other	7	3	43%	<0.5	1
Group Totals	1604	1235	77%	2.8	38
Cross-over Grafts					
Fem-fem	185	176	95%	6.2	30
Fem-pop	37	33	89%	2.2	24
Fem-profunda fem	3	3	100%	2.3	7
Axil-fem	6	6	100%	3.0	16
Fem-distal pop	1	1	100%	7.0	7
Others	4	3	75%	<0.5	2
Group Totals	236	222	94%	5.4	30
Composite Grafts					
C-fem-distal-pop	9	9	100%	2.6	8
C-fem-ant-tib	3	3	100%	6.0	7
C-fem-post-tib	14	13	93%	3.6	7
C-fem-peroneal	4	4	100%	2.5	5
Group Totals	30	29	97%	3.4	8
AV Fistulae	496	416	84%	3.2	22
Forearm	504	478	95%	0.8	18
Upper arm	370	352	95%	3.6	20
Arm	49	39	80%	0.7	10
Leg	101	98	97%	1.0	18
Group Totals	1520	1383	91%	2.3	22
Pulmonary Grafts					
Aorta-pulm shunt	57	48	84%	3.4	27
Pulm reconstrts	3	2	67%	0.0	0
Subclav-pulm	1	1	100%	1.0	1
Group Totals	61	51	84%	3.1	27
Other Arterial Grafts					
Renal artery	18	17	94%	10.7	30
Axil-axil	33	33	100%	4.1	18
Carot-subclav	52	50	96%	8.9	31
Aorto-coronary	15	11	73%	2.3	17
Aorto-renal	25	23	92%	4.0	26
Others	64	62	97%	3.2	29
Group Totals	207	196	95%	5.5	31
Venous Grafts	38	34	89%	7.8	42
Patches	143	135	94%	5.0	30
Totals, All Operations	6291	5469	87%	3.2	42

In 1977, we said: "It is time to consider GORE-TEX reinforced polytetrafluoroethylene (PTFE) vascular grafts as a viable alternative to saphenous vein autografts."

Has experience borne out that claim? Let's take another look.

The GORE-TEX® reinforced PTFE graft works.

If anecdotes were data, we'd have no trouble proving this point. Most surgeons who have used our grafts are high in their praise.

It is, in the majority opinion, the first such graft to come close to the promises made for it.

It is, according to observations and recent *in vitro* studies, relatively thromboresistant. And, when a thrombus forms, it is easy to de-clot.

It is, according to theory but not yet confirmed by data, less likely to present embolism problems later. (A thin, stable intima forms. Whether it's a neointima, pseudointima, or true endothelium is open to debate—but the thinness is the key to logic of the theory.)

It is, in its reinforced form, much more resistant than other versions of expanded PTFE to aneurysmal dilatation. It has high radial or bursting strength and high suture-holding power.

And it is easy to handle and use. Unlike woven or knitted grafts, it will not ravel or fray. And it does not require pre-clotting.

But is it, as we stated earlier, a viable alternative to the saphenous vein?

Yes, *if*.

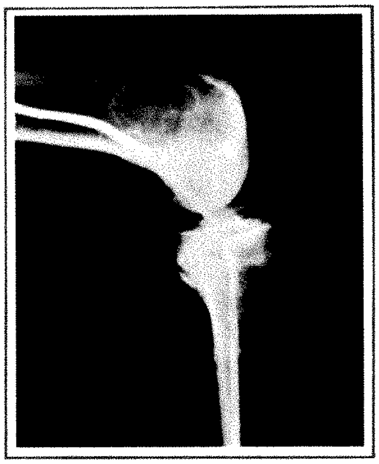
Yes, *if* there is no vein available.

Yes, *if* the vein is "borderline," either in size or condition.

Yes, *if* the patient's condition is such that a prolonged exposure to anaesthesia, or even to the delay in providing the vein, is critical.

Yes, *if* there is the likelihood of cardiac surgery, for which the saphenous vein should be saved.

Given those indications, the GORE-TEX graft is, indeed, a viable alternative to the saphenous vein. But unless those conditions exist, prudence and experience make the saphenous vein the graft of choice.



Arteriogram of a GORE-TEX polytetrafluoroethylene graft during flexion of the knee.

The problem of proof.

As of September 25, 1978, there were approximately 60,000 GORE-TEX vascular graft implants, with over 6,000 follow ups. The overall patency rate was 87%.

Those data, sliced into what we hope are useful pieces, are presented in Table at left.

A close look at the data will reveal one problem: average follow-up times.

They're too short.

The problem is two-fold.

First, we are, of course, dependent on the voluntary cooperation of surgeons for our follow-up data. And we know that if you were to provide all the data that all manufacturers wanted, you would have to spend all of your hours filling out follow-up forms. And, of course, even if you had the time, you can't keep up with all patients over a period of years.

The second part of the problem is statistical. The use of GORE-TEX grafts is increasing so rapidly that we will, for a long time to come, have a far greater number of recent implants than of old ones. (For every GORE-TEX graft implant used three years ago, there are almost 100 used today. Our current reported rate-of-use is approximately 5,000 per month.)

This necessarily skews our data average toward the more recent history. Which is also true for a life table method of data presentation. Even though the maximum experience reported in each category is in the two-to-three *year* range, the weighted averages are more like two-to-three *months.*

More data. More problems. Some suggestions.

On the last page of this advertisement, you'll find a bibliography of published experimental and clinical reports on the use of GORE-TEX vascular grafts, and a coupon for your convenient use.

One problem is that we know the list is not current. Additional papers are always being delivered, and published. If you would like us to keep you up-to-date as new reports appear, check the appropriate box on the coupon.

A more basic problem with these data, and ours, and *all* vascular statistics is the lack of uniformity in reporting. We're supporting efforts to establish some profession-wide protocols begun with a symposium at the 1978 meeting of the American College of Surgeons. If you have any suggestions at all, we'd appreciate them. Just write to us.

GORE-TEX® vascular grafts, in brief.

GORE-TEX vascular grafts are made of expanded, low-density polytetrafluoroethylene (PTFE), reinforced by a strong, fine lattice of the same material wound about the exterior.

GORE-TEX vascular grafts are easy to handle, with excellent resistance to kinking. And they exhibit high suture-holding power. They are, of course, fully biocompatible and, unlike knitted or woven prostheses, do not require pre-clotting.

GORE-TEX vascular grafts for vascular surgery are available in a wide range of diameters.

See next page for free GORE-TEX graft test-pack and complete bibliography, available as reprints.

Free test-pack, reprints.

Submit the handling and suture-holding characteristics of GORE-TEX grafts to the most meaningful test equipment: your own hands. Our test kit, not intended for actual surgery, includes a short length of a GORE-TEX graft and a 6-0 double-armed suture. Try it for yourself. Also, take your choice of reprints of any of the experimental, clinical, and engineering reports listed.

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15. **Summary of Clinical Evaluation Data,** May, 1977 *W. L. Gore & Associates, Inc.*
16. **Long-Term Dilatation Characteristics of GORE-TEX Vascular Grafts: Design Criteria** *W. L. Gore & Associates, Inc.*

Indications and Contraindications.

To sterilize:
Grafts may be sterilized using steam, gas or flash autoclave techniques. Remove the graft from the PVC blister tray and repackage for sterilization. Do not place the package label in contact with the graft during sterilization. Do not place objects on the repackaged graft during sterilization. (See Contraindication #5, 6)

Using steam, autoclave at or above these minimum requirements: 250° Fahrenheit (121° Centigrade) for 20 minutes at 15 p.s.i. Grafts should never be exposed to temperatures greater than 482° Fahrenheit (250° Centigrade).

Using a flash cycle, sterilize at or above these standard minimum requirements: 270° Fahrenheit (132° Centigrade) for 3 minutes at 30 p.s.i. Grafts should never be exposed to temperatures greater than 482° Fahrenheit (250° Centigrade).

Using gas, sterilize according to equipment instructions.

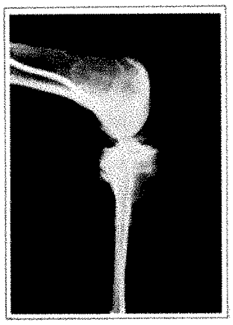
Indications:

1. Use a 5-0 or 6-0 nonabsorbable suture with a cardiovascular needle for best results on graft diameters of 6mm or less. Larger sutures may be used with larger diameter grafts.
2. Intra-operative inspection of anastomoses using irrigant solutions may result in serum leakage when blood flow is established in the graft. To prevent this, care must be taken not to generate syringe pressures sufficient to force irrigant through the graft walls. To do so will alter the hydrophobic (non-wetting) properties of GORE-TEX. (See Contraindication #11)
3. Trim grafts to desired length using sharp surgical instruments. Grafts should be handled with clean forceps or gloves. GORE-TEX grafts are not "elastic." Therefore, proper matching of lengths is essential. If the graft is cut too short, excessive stress may be placed on the sutures and the graft at the anastomosis. (See Contraindication #10)
4. Ensure, when using this graft in blood access applications or where repeated needle punctures of the graft are necessary, that needle puncture sites are spaced apart along the accessible sub-cutaneous length of the graft. Repeated needle puncture of the graft at the same site, or within the same immediate area, may cause mechanical damage to the graft which could lead to hematoma, false aneurysm or true aneurysm. Patients should be carefully monitored to assure that this instruction is followed.

Contraindications:

1. Do not pre-clot the graft.
2. Do not sterilize by irradiation techniques.
3. Grafts should never be exposed to temperatures exceeding 482° Fahrenheit (250° Centigrade).
4. Do not sterilize more than three times.
5. During sterilization, do not place grafts under heavy or sharp objects which might crush the grafts.
6. Do not attempt to sterilize the label attached to the PVC blister tray at high temperatures, as the materials (inks and adhesives) on the label may contaminate any objects in contact with the label during the sterilization cycle.
7. Do not handle graft with ungloved hands. It should be handled only with clean instruments.
8. Do not attempt to resterilize any unused graft portion which has been contaminated with blood or any other foreign material.
9. Do not use absorbable sutures.
10. Do not cut graft while holding under tension. Doing so may cause separation of the outer layer. The GORE-TEX graft is a composite structure consisting of an inner base tube and a thin outer layer which reinforces the base tube to prevent aneurysmal dilatation. Do not use any portion of a GORE-TEX graft which has damage to or separation of the outer layer of the graft.
    Should the outer reinforcing layer become frayed at the end of the graft, do not pull on or peel the outer layer from the base tube. Carefully trim off the portion of the graft where the outer layer is frayed.
11. Do not force irrigating solutions through the graft wall. Doing so may result in serum leakage after blood flow is established.
12. Do not place grafts in any fluid prior to use. Doing so may result in serum leakage after blood flow is established.
13. Do not puncture the graft repeatedly at the same site, or within the same immediate area. (See Indication #4)

GORE-TEX® reinforced vascular grafts.



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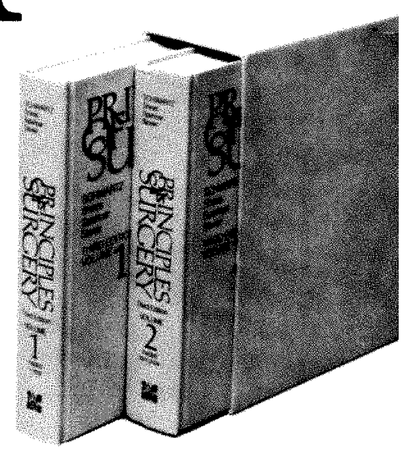

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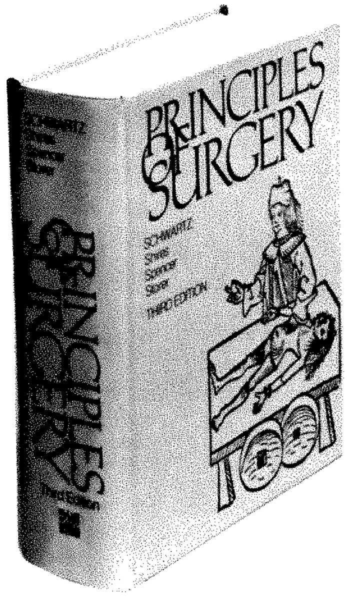

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●
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Here is up-to-the-minute, useable information on the known endocrine syndromes requiring the attention of surgeons and other physicians. The book encompasses all the surgically significant endocrinopathies, both common and rare, all ages of patients, from the newborn to the elderly, and all accepted techniques of clinical and laboratory diagnosis, as well as surgical and conservative management.

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Tablets
PERCOCET®-5 Ⓒ
Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

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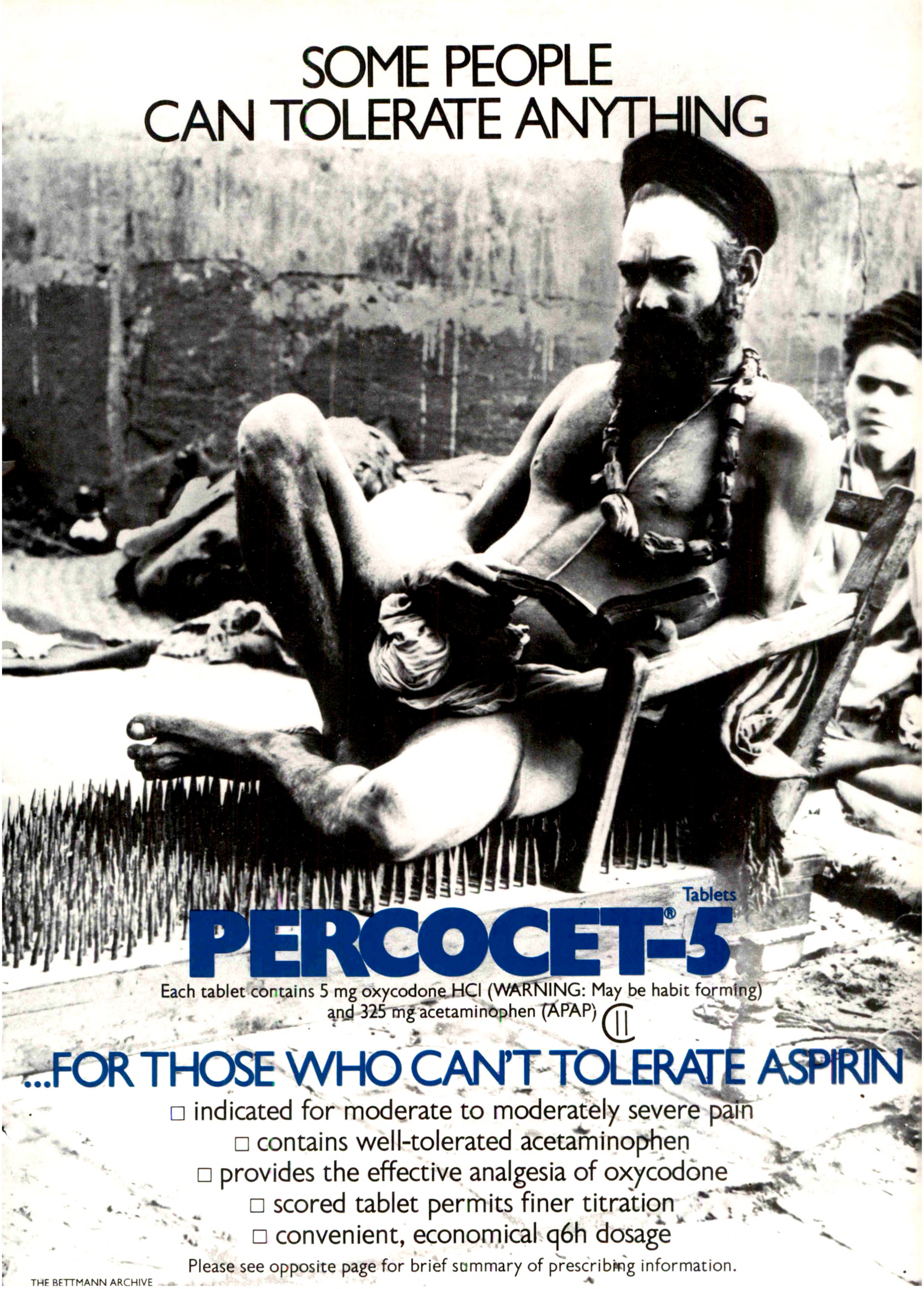

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Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming)
and 325 mg acetaminophen (APAP) CII

...FOR THOSE WHO CAN'T TOLERATE ASPIRIN

☐ indicated for moderate to moderately severe pain
☐ contains well-tolerated acetaminophen
☐ provides the effective analgesia of oxycodone
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Please see opposite page for brief summary of prescribing information.

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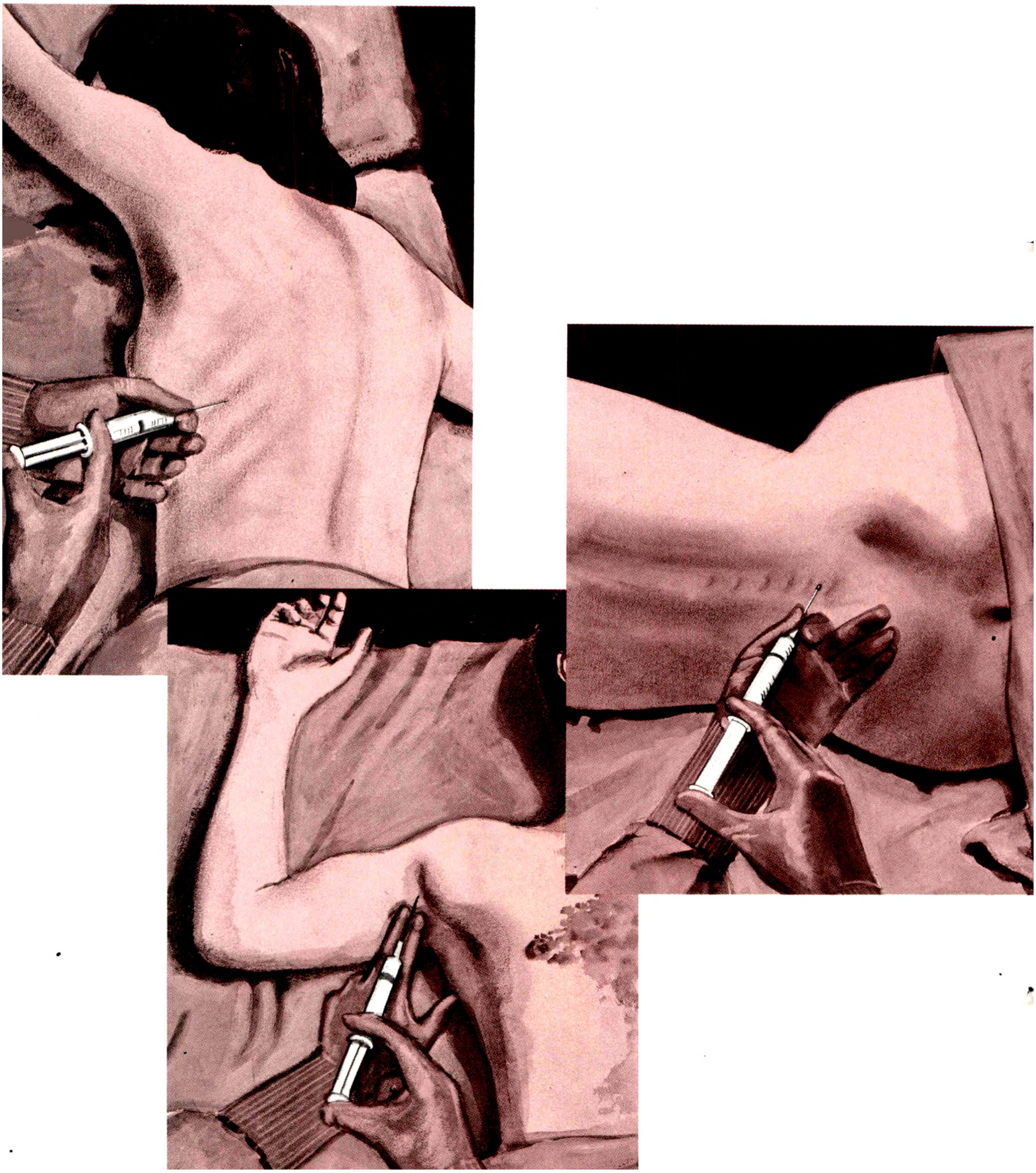


you're missing three other important reasons.

1. More control of motor block

The variety of Marcaine dosage strengths and the ability of Marcaine to provide complete sensory block *with* or *without* significant motor block gives you more control during surgical procedures.[1]

2. Less need for postoperative analgesics

Marcaine with or without epinephrine has been demonstrated to postpone or reduce significantly the need for postoperative narcotics.[1,2]
Results vary with the procedure and the dose administered.

3. Greater postoperative patient mobility

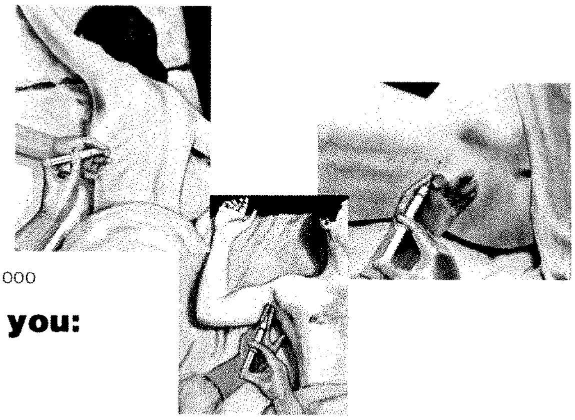
Of 20 patients with flank incision, half were given intraoperative bupivacaine (Marcaine) intercostal blocks. Those who were given Marcaine required less pain medication, were sitting up 2 days earlier, walking 3 days earlier, and took a regular diet 2 days sooner.[3] Ability to cough and breathe deeply was also greater in the Marcaine patients.[3]

The local anesthetic with more reasons to use it than any other.

Marcaine® hydrochloride
brand of
bupivacaine hydrochloride with or without epinephrine 1:200,000

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on the next page. As with any local anesthetic, inadvertent intravascular injection may result in general convulsions.

Please see following page for full prescribing information.



Marcaine® hydrochloride
brand of
# bupivacaine hydrochloride
with or without epinephrine 1:200,000

The long-acting local anesthetic that gives you:

1. **More Control of Motor Block**
2. **Less Need for Postoperative Analgesics**
3. **Greater Postoperative Patient Mobility**

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References: 1. Moore DC, Bridenbaugh LD, Thompson GE, et al: Bupivacaine: a review of 11,080 cases. *Anesth Analg* 57: 42-53, 1978. **2.** Lund PC, Cwik JC, Vallesteros F: Bupivacaine—a new, long-acting local anesthetic agent: a preliminary clinical and laboratory report. *Anesth Analg* 49:103-114, 1970. **3.** Noller DW, Gillenwater JY, Howards SS, et al: Intercostal nerve block with flank incision. *J Urol* 117: 759-761, 1977.

BREON
BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

FORMULA

PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl) %	mg./ml.	**Epinephrine* (as bitartrate)** Dilution	Methyl-paraben mg./ml.	Sodium Bisulfite mg./ml.	Thio-glycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.	Sodium Bisulfite mg./ml.	Thio-glycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.50	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.50	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						0.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

Viokase® costs your patients less than other pancreatic preparations

4x N.F. Protease
6x N.F. Amylase
10 x N.F. Lipase
(whole pancreas)

Twenty-Five Year Veteran

NDC 668-0013-01
Viokase®
Description: VIOKASE is a pancreatic enzyme concentrate of porcine origin containing standardized lipase, protease and amylase activities plus esterases, peptidases, nucleases and elastase.
CAUTION: Federal Law Prohibits Dispensing Without Prescription
100 TABLETS
325 mg EACH
VIOBIN

in the management of exocrine pancreatic deficiencies

The effectiveness of Viokase is confirmed by over twenty-five years of clinical experience...and it still costs your patients less than other pancreatic preparations. Current literature[1,2] documents the use of Viokase as a digestive aid in cystic fibrosis and in exocrine pancreatic deficiencies usually due to chronic pancreatitis, pancreatectomy or obstruction in the pancreas caused by malignant growth.

1. Kafka, E. and Klaser, H.: "Pancreatic Disease", *Postgraduate Medicine*, 57: 140-145, 1975.
2. Long, W.B. and Weiss, J.B.: *Gastroenterology*, 67:920-925, 1974.

VIOKASE®
(pancreatin)

Description: VIOKASE is a pancreatic enzyme concentrate of porcine origin containing standardized amylase, protease and lipase activities plus esterases, peptidases, nucleases and elastase.

The enzyme potency of the tablets and powder are:

	Each 325 mg. Tablet	Each 0.75 gram (⅓ teaspoonful)
Lipase, N.F. Units	6.500	15.000
Protease, N.F. Units	32.000	75.000
Amylase, N.F. Units	48.000	112.500

Under conditions of the N.F. test method (in vitro) VIOKASE has the following total digestive capacity:

	Each 325 mg. Tablet	Each 0.75 g. Powder
Dietary Fat	23	53 grams
Dietary Protein	32	75 grams
Dietary Starch	48	112 grams

VIOKASE Tablets are not enteric coated.

Indications: As a digestive aid in cystic fibrosis and in exocrine pancreatic deficiencies usually due to chronic pancreatitis, pancreatectomy or obstruction in the pancreas caused by malignant growth.

Administration and Dosage:
Powder: Dosage to patients with cystic fibrosis: ⅓ teaspoon (0.75 grams) with meals.

Tablets: Dosage to patients with cystic fibrosis or chronic pancreatitis —1 to 3 tablets with meals. For aiding digestion in patients with pancreatectomy or gastrectomy—1 to 2 tablets taken at 2-hour intervals, or as directed by physician.

Caution: Federal law prohibits dispensing without prescription.

Warnings: Avoid inhalation of powder.

Precautions: Use with caution in patients known to be allergic to pork protein.

How Supplied:
Powder: Bottles of 4 ounces and 8 ounces
Tablets: Bottles of 100 and 500

Literature Available: Complete literature available upon request including information on BEEF VIOKASE DERIVED FROM BEEF PANCREAS FOR THOSE EXCEPTIONAL PATIENTS ALLERGIC TO PORK.

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Not All Postsurgical Patients Should Receive Potent Injectable Narcotics

CAUTION

In patients with decreased respiratory reserve, morphine and related narcotics must be used with great caution.

High Risk Patients

- Severely obese patients
- Patients with kyphoscoliosis
- Patients with chronic cor pulmonale
- Emphysematous patients
- Asthmatic patients

Many patients with such conditions are already utilizing compensatory mechanisms, such as increased respiratory rate. Many may have decreased sensitivity to elevated plasma CO_2 stimulation. The further imposition of the depressant effects of narcotics can be disastrous.

Consider

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of

pentazocine lactate injection, NF

Talwin shows infrequent occurrence of certain adverse effects* as:

- Respiratory depression (see below)
- Circulatory depression
- Shock
- Tachycardia
- Urinary retention

The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g. from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

There have been instances of psychological and physical dependence on Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. Patients with a history of drug dependence should be under close supervision while receiving Talwin. In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

For immediate pain control without many of the risks of narcotic analgesics:

Talwin®

30 mg. parenterally q. 3 to 4 hours.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

*See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of
pentazocine lactate injection, NF

Relieves pain of a moderate to severe nature.

Please consult full prescribing information before prescribing. A summary follows:
Talwin is intended for the relief of moderate to severe pain. 30 mg. is usually as effective an analgesic as morphine 10 mg. or meperidine 75 to 100 mg. The duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15 to 20 minutes after intramuscular or subcutaneous injection and within 2 to 3 minutes after intravenous injection. Talwin is a weak narcotic antagonist with sedative activity. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

CONTRAINDICATION

Hypersensitivity to pentazocine.

WARNINGS

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, animal studies have demonstrated that Talwin is tolerated less well subcutaneously than intramuscularly.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

PRECAUTIONS

The possibility that Talwin may cause respiratory depression should be considered. Talwin should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

ADVERSE REACTIONS

The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face, toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

Adults, Excluding Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg.

See Warnings in package insert as to recommended sites and routes of administration.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

OVERDOSAGE

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

HOW SUPPLIED

Uni-Amp®—Individual unit dose ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in boxes of 25.

Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in (nested) boxes of 25.

Each 1 ml. contains pentazocine lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing pentazocine lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

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Preoperative Estimation of Run Off in Patients with Multiple Level Arterial Obstructions as a Guide to Partial Reconstructive Surgery

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Preoperative measurements of direct femoral artery systolic pressure, indirect ankle systolic pressure and direct brachial artery systolic pressure were carried out in nine patients with severe ischemia and arterial occlusions both proximal and distal to the ingvinal ligament. The pressure-rise at the ankle was estimated preoperatively by assuming that the ankle pressure would rise in proportion to the rise in femoral artery pressure. Thus it was predicted that reconstruction of the iliac obstruction with aorta–femoral pressure gradients from 44 to 96 mm Hg would result in a rise in ankle pressure of 16–54 mm Hg. The actual rise in ankle pressure one month after reconstruction of the iliac arteries ranged from 10 to 46 mm Hg and was well correlated to the preoperative estimations. In conclusion, by proper pressure measurements the run-off problem of multiple level arterial occlusions can be evaluated. Thus the result of successful partial reconstruction can be assessed preoperatively.

PATIENTS WITH REST PAINS and toe ulcerations on the foot, caused by severe occlusive arterial disease, are in urgent need of arterial reconstructive surgery in order to avoid amputation.

These patients typically have arterial obstructions at two or more levels along the arterial tree. It is well documented that only proximal procedures should be made in cases where only a partial reconstruction is attempted.[4] Thus the question is whether such a partial reconstruction will suffice to save the leg. This is dependent on the blood flow run off to the foot. The run off is determined by a series of obstructions to blood flow and each obstruction causes a pressure drop. In the present paper we have "translated" the blood flow run-off into a series of segmental pressure drops. The systolic pressure drop from the aorta to the common femoral artery and from the aorta to the foot have been subjected to several studies and seem technically to offer a possibility for such a segmental study.[2,3,5,8]

Materials and Methods

Nine patients with ischemia and rest pains for more than two months were studied. Eight had small ischemic ulcerations. The average age was 65 years (range 57–74). The blood pressure on the leg was measured by the strain-gauge technique at the ankle and at the first toe.[1] All patients had marked distal hypotension with systolic toe blood pressures ranging from 0 to 30 mm Hg and arterial occlusions or severe stenosis both proximal and distal to the inguinal ligament as indicated by angiograms.

Segmental systolic blood pressure measurements were carried out on a separate day with the recumbent patient in a thermoneutral room. The blood pressure in the femoral artery, *viz.* in between the proximal and distal arterial occlusions was measured directly. The systemic blood pressure was also measured directly by cannulation of the brachial artery. The systolic ankle blood pressure was measured indirectly by strain-gauge technique. A Doppler-shift pencil probe was used in puncturing the femoral artery in which no pulsations could be felt. Detailed supplementary angiograms were also made through the femoral catheter.

Prediction of the Rise in Distal Blood Pressure by Reconstruction of the Proximal (Iliac) Arterial Occlusion

From the experiences with induced hypertensive treatment[7] in more than 100 patients of the same category during the last ten years, we are led to assume that a rise in systolic femoral artery pressure after a proximal reconstruction would result in a proportional rather than parallel increase of ankle systolic pressure. Thus, if the systemic systolic blood pressure is 160 mm Hg, femoral artery systolic blood pressure is 80 mm Hg and

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Submitted for publication: May 7, 1977.

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TABLE 1. *Pre- and Postoperative Pressures and the Estimated Pressure Increase at the Ankle (mm Hg)*

	Systolic Blood Pressure Preoperatively			Systolic Blood Pressure One Month Postoperatively			Segmental Measured Systolic Pressure Gradients		Systolic Ankle Pressure Increase	
	Arm	Ankle	L. Toe	Arm	Ankle	L. Toe	Proximal	Distal	Estimated	Measured
x̄	136	45	13	138	78	30	70	31	34	33
SD	21	17	11	29	12	12	20	11	13	12
Range	115–180	30–60	0–30	100–190	63–99	18–50	44–96	11–43	16–54	10–46
p				NS	$p < 0.01$	$p < 0.01$				NS

ankle systolic pressure is 30 mm Hg, then a perfect reconstruction of the arteries above the ligament will increase the pressure in the common femoral artery to 160 mm Hg, *i.e.* by 100%. The ankle pressure too will then be expected to increase by 100%, and hence a rise in ankle pressure to about 60 mm Hg could be predicted.

Results

The success of partial reconstruction was judged by the appearance of ipsilateral pulsation in the femoral artery. The distal pressures increased immediately after the operation and usually a further increase was seen on the tenth day. After one month the patients were ambulant and the distal pressures had stabilized.

Table 1 lists the arm blood pressure, the ankle and toe pressure recorded preoperatively as well as one month postoperatively, the results of the segmental pressure measurements, together with the estimated and measured pressure increase at the ankle. The systolic pressure-drop from the systemic circulation to the femoral artery was on average about two time the systolic pressure-drop from the femoral artery to the ankle. Postoperatively the pressure at the ankle increased on the average by 33 mm Hg and the toe pressure by 17 mm Hg. The estimated increase in ankle pressure to be expected from successful proximal reconstruction averaged 34 mm Hg. The highly significant correlation of estimated and observed rise in ankle systolic pressure is seen in Figure 1.

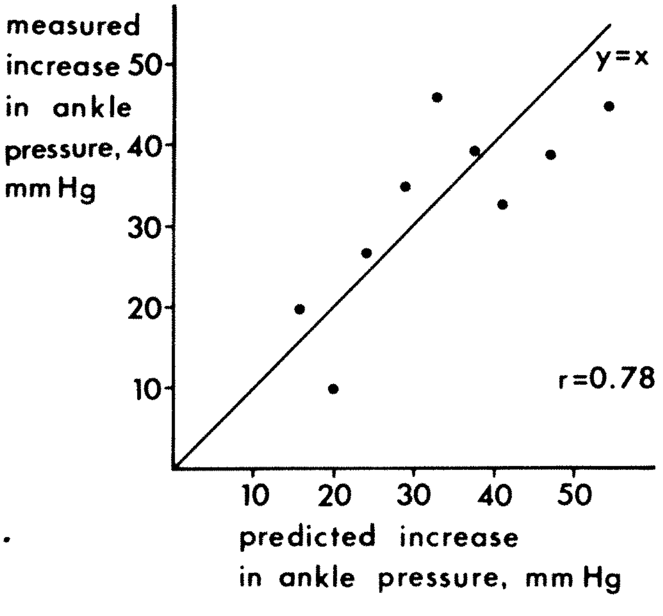

FIG. 1. The ankle pressure rise estimated from the segmental pressure measurements and the actual rise in ankle pressure before and after operation.

Although the mean value of the toe pressure rose to about 30 mm Hg postoperatively, four patients still had toe pressures of respectively 18, 18, 19 and 20 mm Hg. However, also in these patients the rest pain disappeared, and the ischemic ulcers healed gradually over some months concomitant with a slight rise in toe pressures. We have not encountered complications to the preoperative segmental pressure measurements.

Discussion

From the results it appears that our mode of predicting the rise in ankle pressure was satisfactory. But, of crucial importance for the healing of the ischemic foot ulcer, usually localized to the toes, is the pressure at the site of the ulcer. Hence the important distal pressure is the toe blood pressure. This has recently been documented in our department by Holstein et al.[6] who followed 66 patients with chronic ischemic foot ulcerations for up to two years. Healing took place in 40 patients out of 44 patients who had toe pressures above 20 mm Hg, but only in two patients out of 22 patients, who had toe pressures below 20 mm Hg. These results confirm our daily experiences that rest pain predominantly occurs in patients with toe pressure below 20 mm Hg, and that the rest pain disappears at the same time as the toe pressure rises above 20 mm Hg, either by spontaneous remissions or by induced hypertensive treatment.[7]

From a larger series of 35 vascular reconstructions (P. Lund and K. H. Tønnesen, to be published) we know that the toe pressure-rise is 10–15 mm Hg less than the rise in ankle pressure. The same observation was also made in the present series where the average toe pressure after operation rose from 13 to 30 mm Hg whereas the average ankle pressure rose from 45 to 78 mm Hg, *i.e.* the rise in toe pressure was 16 mm Hg less than that of the ankle.

On the basis of these data the postoperative toe pressure can be estimated roughly as follows: from the segmental pressure measurements the predicted rise in ankle pressure is calculated; 15 mm Hg is subtracted to get the estimated rise in toe pressure. When adding this to the preoperative toe pressure you find the estimated postoperative toe pressure. This pressure should exceed 20 mm Hg following successful reconstruction.

It is seen from Figure 1 that the predicted increase in ankle pressure in three of the patients was only 15 to 30 mm Hg. Therefore, the postoperative rise in toe pressure could only be expected to be 5–15 mm Hg. However, the preoperative systolic blood pressure on the toes in these three patients was between 10–20 mm Hg. Therefore, partial proximal reconstruction was considered indicated because only a marginal toe pressure rise was considered necessary to save the feet of the patients in question. In these three borderline cases the proximal pressure gradients were 44, 46 and 48 mm Hg, and the distal gradients were 36, 11 and 28 mm Hg respectively. For all patients the average proximal gradient was 70 mm Hg and the average distal gradient was 31 mm Hg. A working rule may be derived from all these figures, in order to avoid operations on borderline cases: The proximal gradient should be more than 30 mm Hg.

We have examined two patients not included in the material with multiple level-occlusions who had proximal pressure gradients of only 10 and 30 mm Hg and distal pressure gradients of 60 and 125 mm Hg respectively. The calculation showed that successful operations would not result in a measurable pressure increase in the toe. Therefore these two patients were not operated upon.

The above arguments constitute the rationale behind the preoperative segmental pressure measurements. It is *not* correct to argue "we can always explore the proximal arteries and remove any minor proximal obstruction: At worst no harm is done, at best a small improvement is obtained, therefore let us give the patient the benefit of even this small possible improvement:" On the contrary, a temporary but occasionally disastrous worsening of symptoms may occur.

With this added comment, our data support the growing conviction that properly performed partial surgery can be most rewarding. Provided it is known, what can be expected from the operation and thus the indications and also the limitations of partial reconstructive surgery. In a nutshell, when one should operate and when one should not.

Acknowledgment

The authors wish to thank Professor E. Hart-Hansen, Mr. Per Holstein, Mr. P. Tønnesen, the Department of Orthopedic and Vascular Surgery, Johs. Præstholm, head of the Department of Radiology and dr. Per Lund, dr. S. L. Nielsen, and dr. J. P. Barras, The Department of Clinical Physiology for their encouraging participation in the present study, and Niels A. Lassen, head of the Department of Clinical Physiology, and chief surgeon Hugh Dovey, the Department of Orthopedic and Vascular Surgery for constructive criticism in the preparation of the manuscript.

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Combination Chemotherapy Followed by Skin Grafts in the Management of Locally Advanced Breast Cancer

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A combined modality approach to the treatment of locally advanced, ulcerating carcinoma of the breast is discussed. The beneficial effects of combination chemotherapy have been amplified by split thickness skin grafts at the site of a large skin deficit, resulting in successful wound palliation. Criteria for assessing likelihood of graft acceptance by an ulcerating wound in the presence of local neoplastic disease are emphasized.

LOCALLY ADVANCED, ulcerating carcinoma of the breast poses a particularly difficult management problem. Often, the disease is so extensive that palliative radiation therapy or operation is not feasible, and combination chemotherapy is the most appropriate treatment. Although the objective response rates to antineoplastic therapy are between 50–80,%[1-3]drug-induced leukopenia and thrombocytopenia place the patient at risk for infection and/or hemorrhage. The case described below is that of a woman with bilateral ulcerating, fungating breast cancer, and demonstrates the beneficial effects of split thickness skin grafts subsequent to combination chemotherapy.

Case Report

A.S. is a 76-year-old, white woman referred to the Oncology Service for the treatment of Stage IV breast cancer. The patient initially noted bilateral breast swelling in September 1975, and she neglected it. In August 1976, she was referred to a radiotherapist for evaluation of bilateral fungating breast lesions. Biopsy of the left breast mass showed mucinous adenocarcinoma. There was no evidence of bony or visceral metastases. Due to the extent of disease, operation and radiotherapy were not considered appropriate, and diethylstilbesterol, 5 mg p.o. t.i.d. was begun by her primary physician. In December 1976, the patient was referred to the Oncology service because of progressive skin involvement (Fig. 1). On physical examination, the left breast was completely replaced by necrotic, ulcerating tumor which was bleeding, friable and covered with purulent material. The right breast was partially replaced by the same process. There were many skin nodules which extended from the breast masses to the anterior abdominal wall. Multiple 2 × 3 cm firm, fixed lymph nodes were noted in the axillae bilaterally. The physical examination was otherwise normal. The complete blood count, liver function tests, calcium, phosphorous and carcinoembryonic antigen were within normal limits. The patient was considered to have Stage IV Breast Cancer (T4N2M1) with extensive skin and lymph node involvement. The diethylstilbestrol was discontinued, and chemotherapy with Cytoxan (1 mg/M^2 days 1–14), Methotrexate (40 mg/M^2 days 1 + 8) and 5-FU (400 mg/M^2 days 1 + 8) was administered. After three full courses of Cytoxan, Methotrexate and 5-Fluorouracil (CMF) much of the tumor in the area of the breasts had sloughed, leaving weeping, erythematous, infected tissue. The skin nodules and axillary adenopathy had decreased in size as well. In March 1977, one week before she was to receive her fourth course of chemotherapy, the patient developed a high fever, dyspnea, disorientation, and was found to have bilateral pneumonia. The white blood count was 3,700 with 84% neutrophils. Both blood and sputum cultures grew coagulase positive Staphylococci and *Pseudomonas aeruginosa*. The patient required endotracheal intubation for several days and received oxacillin, gentamycin and carbenicillin in combination. The chest wound culture was also positive for Staphylococci and Pseudomonas. Wound treatment was begun with 0.25% acetic acid dressings changed every four hours. The patient made a slow but complete recovery from the sepsis and pneumonia. The chest wound infections resolved, the granulation tissues appeared healthier, (Fig. 2) and evidence for epithelialization was noted. During the hospitalization the patient received a fourth course of CMF which resulted in leukopenia, but no recurrence of invasive bacterial infection was noted. Biopsy of nodules surrounding the wound were positive for adenocarcinoma.

On June 3, 1977, under local anesthesia, (½% xylocaine with epinephrine 1:200,000), split thickness skin grafts, about .0010 inches in thickness were harvested from the right thigh. Skin grafts were applied to both breasts and immobilized in place with Steri-strips®. (Fig. 3) There were not operative or postoperative complications and 95% "take" of the skin grafts was noted.

From June 1977 through April 1978, the patient has received nine additional courses of CMF with periodic dose reduction for leukopenia. The skin and axillary disease are stable without clinical or laboratory evidence of dissemination, and both grafts remain intact. There have been no episodes of infection or pain and wound care is limited to soap, water and a bandaid (Fig. 4).

Discussion

Control of locally advanced, incurable breast cancer is often difficult to achieve. When cutaneous ulceration

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Submitted for publication: April 28, 1978.

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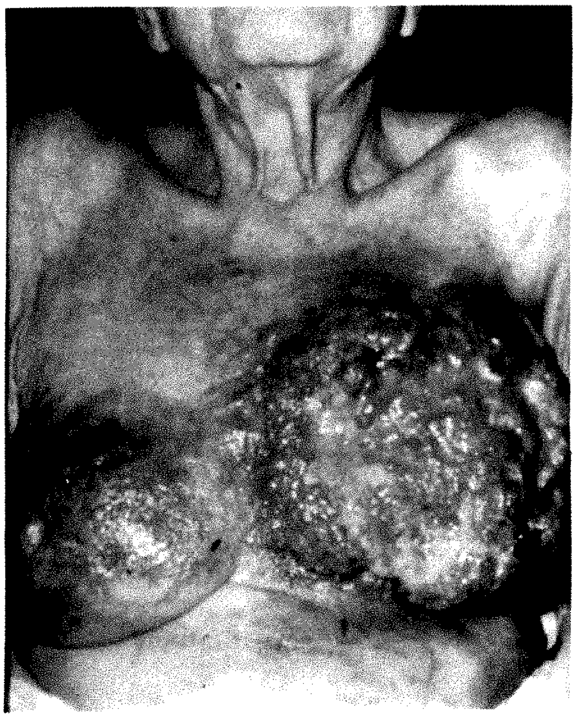
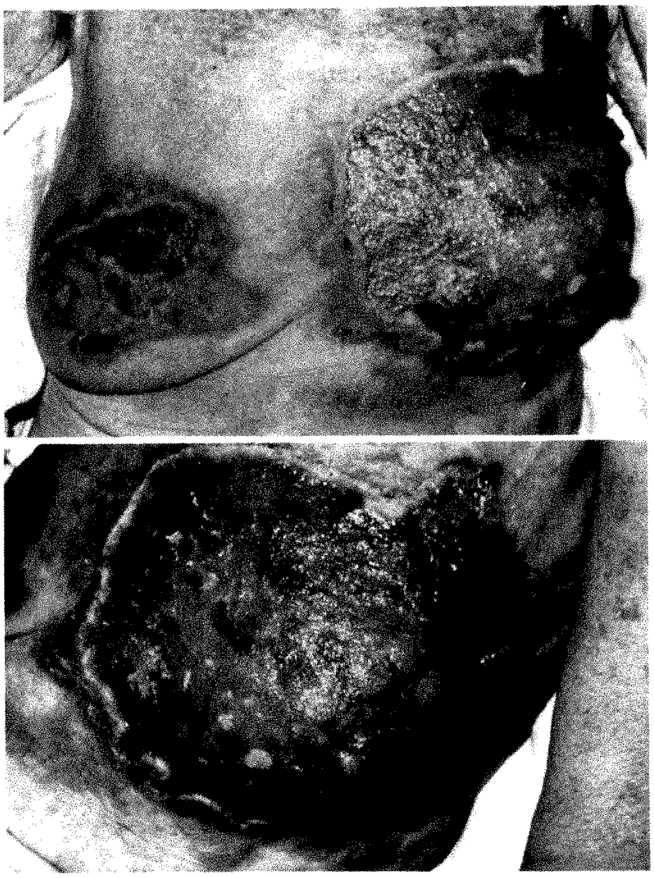


FIG. 1a. Clinical appearance at the time of presentation: frontal view.



FIGS. 2a and b. Clinical appearance of the breasts after 3 months of combination chemotherapy. (a, top): Frontal view. (b, bottom): Left Breast.

due to erosion by tumor ensues, patients not amenable to radiation therapy are left with painful, infected, malodorous lesions that become a source of chronic blood loss and a portal for life-threatening systemic infection. Whether this occurs as a presenting manifestation of the disease, or whether it follows failure of local treatment or resistance to current therapy, it poses problems of pain and infection. This occurs in as many as one third of all breast cancer cases.[5] Estrogen receptor positive patients can be treated with hormones. The rate of objective remission for hormonal therapy is 55–60%[6] whereas 50–100% of patients respond to combination chemotherapy.[1–3] As in the case under discussion, the patients who respond to treatment may nonetheless be left with a significant cutaneous deficit that serves as a nidus for an invasive and life threatening infection. These lesions may cause severe pain which may be exacerbated by frequent changes of dressings. Hypertrophic granulation tissue

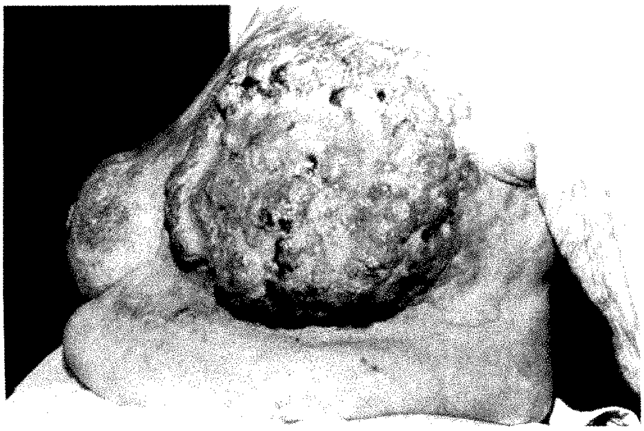


FIG. 1b. Same patient as Figure 1A: left breast.

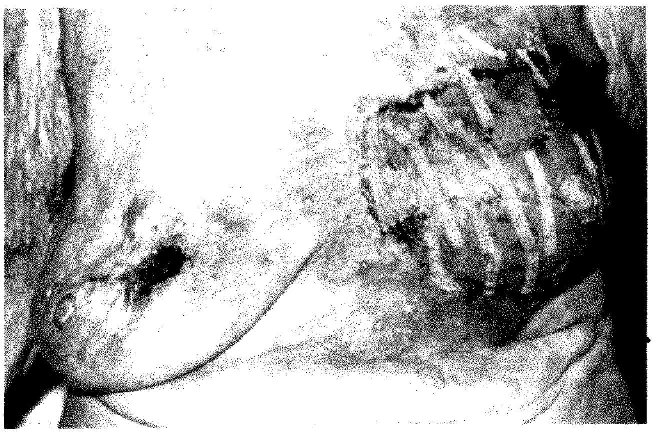


FIG. 3. Seventy-two hours after application of split thickness skin grafts.

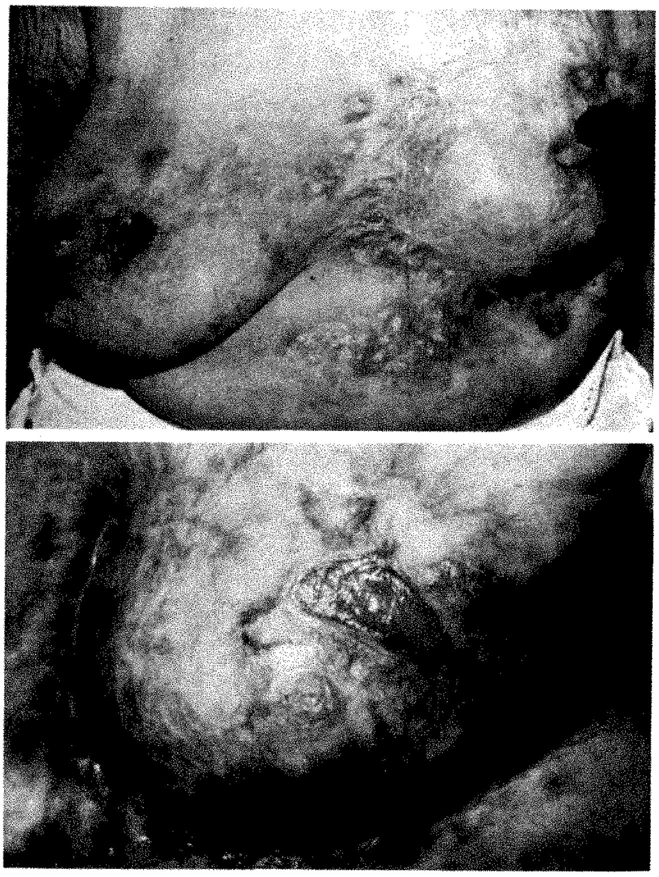


FIG. 4. Nine months after application of the skin grafts. (a, top): Frontal view. (b, bottom): Left breast.

encourages the entrance and growth of bacteria, while protein, electrolyte and fluid loss compound an often catabolic state. Given these circumstances, despite the presence of residual tumor, skin grafting may provide excellent wound palliation. The extent of the operation is minimal; the operative time required to complete the procedure is often less than one hour. Since the split thickness graft is taped into place without the use of sutures, there is no need for local anesthesia to the tumor area. The risk of altering the host-tumor relationship with sutures and needles is thereby minimized. The whole procedure can be done under local anesthesia to the donor site only. Although unorthodox in concept, grafting can be carried out successfully despite the presence of active neoplastic disease.[4,7] The acceptance of the skin graft will depend on the vascularity of the recipient bed and not on the presence or absence of neoplastic disease. In theory, any wound producing granulation tissue has the inherent vascularity necessary to support a skin graft. In the case presented, subsequent to reduction in tumor mass secondary to chemotherapy, sufficient vascularity manifested itself to assure a "take" of the skin graft.

This experience suggests that large residual skin deficits following systemic therapy for locally advanced breast cancer may be successfully treated by the use of split thickness skin grafting.

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Alimentary Tract Duplications in Children

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This report reviews the experience with 78 alimentary tract duplications found in 64 patients over a 40 year period at the Children's Hospital of Pittsburgh. Ten patients had the duplication discovered at autopsy. Multiple duplications were found in 15% of patients. The symptoms and physical findings of a duplication varied with location, size and mucosal pattern. About one-fifth of the duplications contained ectopic mucosa, usually gastric. Two-thirds of the patients were diagnosed prior to one year of age. Vertebral anomalies, as a clue to the presence of the lesion, were present in 15% of the patients. The most common indications for surgery included a mediastinal or abdominal mass, intestinal obstruction, and gastrointestinal bleeding. The results of surgery were favorable, with a mortality of 20%. Surgical complications accounted for six deaths, while four children died of severe associated anomalies. Three others died without surgical treatment, but with symptoms from the duplication.

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DUPLICATIONS OF THE ALIMENTARY TRACT are congenital lesions, cystic or tubular in shape, and composed of muscular walls with gastrointestinal mucosal lining. They are almost invariably adjacent to the alimentary tract, may communicate with the lumen, and may be multiple. These lesions can occur throughout the alimentary tract, but lesions of the tongue[10] and pharynx are much less common than those originating in the esophagus, stomach, small bowel and colon.

In 1884, two years prior to his classical description of appendicitis, Reginald Fitz used the word "duplication" to describe what he thought were remnants of the omphalomesenteric duct.[7] The terms "enterogenous cyst," "ileum duplex," "giant diverticula" and "unusual Meckel's diverticula" have been used to describe congenital cystic or tubular abnormalities of the gastrointestinal tract. In 1937, W. E. Ladd, reporting ten cases, used the phrase "duplications of the alimentary tract . . . in the hopes of simplifying the nomenclature."[12] Gross, et al. supported the use of the term "duplication" in their classic work in 1952 in which they explained the inaccuracy of terms.[10]

Material

We have reviewed 78 duplications in 64 patients seen at Children's Hospital of Pittsburgh from 1935 to 1975. Ten patients had multiple duplications. Five patients were black and 59 were Caucasian. Included in this report are 27 previously reported patients.[13,18]

Fifty-two of the 64 patients had either symptoms or physical findings leading to the surgical discovery of the duplication. Six patients had the diagnosis made at autopsy, and four of the thoracic duplications were unsuspected until discovered by chest x-ray. The duplications were diagnosed in 54 patients (85%) prior to age two years, and in 39 patients (60%) prior to age six months. However, a significant number of patients may not become symptomatic until adult life.[1]

This series includes 16 thoracic, 12 gastric or duodenal, 34 jejunal or ileal, 14 colonic or appendiceal, and two retroperitoneal duplications (Fig. 1). The embryology, symptomatology, diagnosis, therapy and results vary with the anatomical location of the lesion.

Clinical Pictures

Thorax

Thoracic duplications are best explained by the endodermal–ectodermal adhesion,[16] or the split notochord theory. An embryological error allowing endoderm to herniate through the notochord at three to six weeks of development is currently the best explanation for posterior mediastinal duplications. Vertebral defects are often associated with these duplications as part of the embryological error (Fig. 2).[4]

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Submitted for publication: March 26, 1977.

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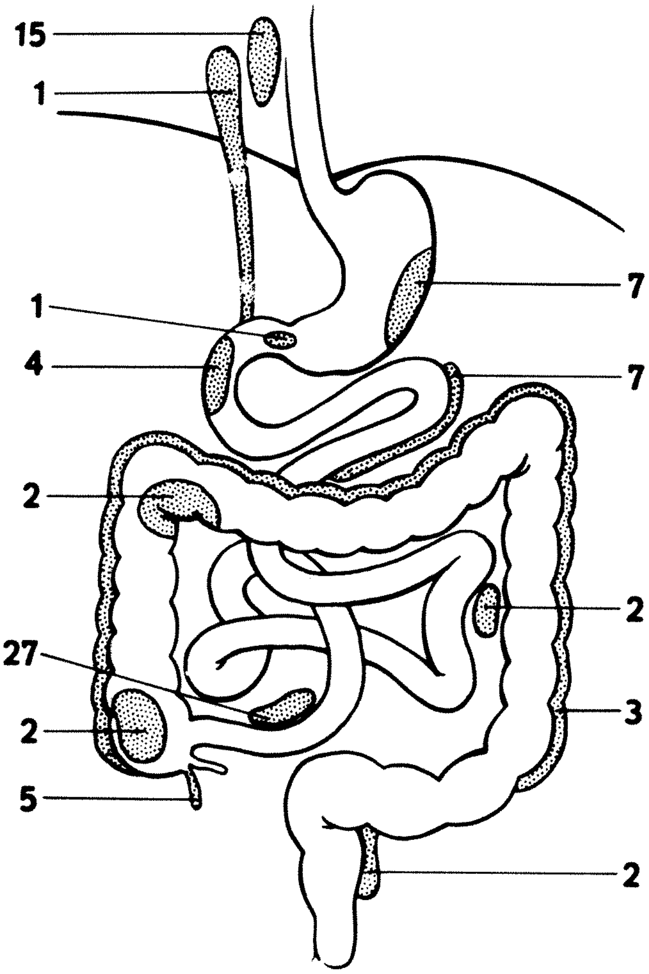

FIG. 1. Diagrammatic location of the 78 duplications.

There are 16 thoracic duplications in this report. Most often, respiratory symptoms led to the diagnosis (Table 1). Three infants presented with severe respiratory obstruction on the first day of life. Haller[11] has stressed that duplications should be considered in the differential diagnosis of severe respiratory obstruction in the newborn. Duplications are second only to neural tumors as a cause of posterior mediastinal masses in children. Ectopic gastric mucosa was present in seven of these cases. Peptic ulceration can cause pain, bleeding, or rarely perforation of the duplication, and one of our patients had anemia and one had hematemesis. Spinal cord compression is rare in spite of severe vertebral anomalies.

Chest roentgenograms usually show the duplication as a posterior mediastinal mass. Occasionally, a barium swallow shows esophageal compression from the cyst. Because of the incidence of ectopic gastric mucosa, it is sometimes possible to diagnose duplications preoperatively by the use of a technetium scan.[6]

Three of the 16 cases had hemivertebrae (Fig. 2). Only one of the 16 cases had an abdominal extension of the duplication, and two other patients with thoracic duplications had separate jejunal duplication.

Of the 15 patients undergoing surgical resection, 12 had a right thoracotomy and three a left; others have also noted the preponderance of right-sided lesions.[10] Operation is undertaken because of the possible complications of bleeding, perforation, respiratory obstruction, and difficulty in differentiating the mass from a posterior mediastinal malignancy. If there is a common cyst-esophagus wall, only the cyst mucosa of the shared wall need be resected while removing the remainder of the mass *in toto*. Care should be taken to be sure that there is no neuroenteric communication.

One patient died of pneumonia at age two weeks without operation and a duplication between the esophagus and trachea was found at autopsy. Another patient died postoperatively of aspiration while a third has severe brain damage secondary to aspiration. The other 13 patients underwent resection of the duplication without problems (Table 1).

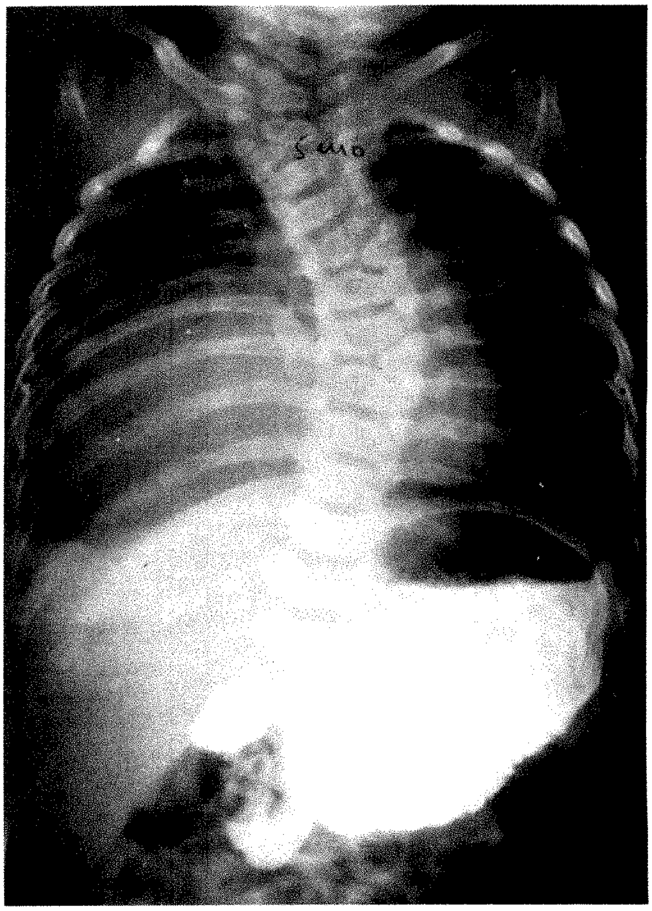

FIG. 2. Hemivertebrae in five-month-old with right-sided thoracic duplication.

TABLE 1. *Thoracic Duplications*

Pts.	Age	Symptoms	Size (cm)	Ectopic Mucosa	Result
1.	1 day†	Respiratory Obstruction	5 × 3	Gastric	Postop aspiration; recovery
2.	1 day*	Respiratory Obstruction	6 × 3	Adrenal Cortex	Resection; recovery
3.	1 day	Respiratory Obstruction	3	—	Died without operation
4.	2 day	Aspiration	3	—	Died 2 mos. postop aspiration
5.	6 wks	Pneumonia	4.5	—	Resection; recovery
6.	4 mos	Pneumonia	4	Gastric	Resection; recovery
7.	4 mos	Pneumonia	4	Gastric	Resection; recovery
8.	6 mos	No symptoms	3.5	Gastric	Resection; recovery
9.	10 mos†	Anemia	2.5	Gastric	Resection; recovery
10.	11 mos*†	No symptoms	6 × 5	—	Resection; recovery
11.	19 mos	Wheezing	7	Gastric	Resection; recovery
12.	8 yrs	Cough	4	—	Resection; recovery
13.	8 yrs	Pain	11 × 6	Gastric	Resection; recovery
14.	10 yrs	Hematemesis	2.5	—	Resection; recovery
15.	11 yrs	No symptoms	16 × 3	—	Resection; recovery
16.	16 yrs	No symptoms	7	—	Resection; recovery

* Also had separate jejunal duplication

† Hemivertebrae

TABLE 2. *Gastroduodenal Duplications*

Patients	Age	Symptoms	Size (cm)	Location	Result
1.	7 mos	None (autopsy)	1	Stomach	Autopsy finding
2.	2 mos	Obstruction Masses Melena	5 3 & 3	Stomach Duodenum	Died 2° to perforation of gastric duplication
3.	1 mo	Obstruction Masses	4 × 3 2 × 1	Stomach Stomach	Resection; recovery
4.	2 days	Vomiting Mass Jaundice	2.5	Duodenum	Died after resection
5.	3 mos	Mass	4	Stomach	Resection; recovery
6.	2 wks	Vomiting Mass	4 × 2	Stomach	Resection; recovery
7.	3 wks	Vomiting "olive"	1.5	Pylorus	Excision; recovery
8.	1 mo	Mass	3	Duodenum	Roux Y; recovery

Stomach and Duodenum

Gastric and duodenal duplications were once considered quite rare, but recent reviews report over 50 examples in each location.[13] Pyloric duplications are extremely rare with only three reported up to 1970.[9]

The etiology of duplications of this area is unknown, but the diverticulum theory of Lewis and Thyng[14] and the Bremer[3] theory of failure to recanalize are often mentioned; neither completely explains the origin. It is of interest that gastric duplications are twice as common in girls;[2] three of our four were found in girls.

Vomiting, secondary to partial or complete obstruction and an upper abdominal mass are almost always present in the clinical course (Table 2). The diagnosis can sometimes be made by an upper G.I. series which may shown an extrinsic gastric mass (Fig. 3) and depression of the transverse colon. Peptic complications of pain, bleeding and perforation, as well as increased gastrin secretion, have been reported. The one pyloric duplication was found after a preoperative diagnosis of hypertrophic pyloric stenosis.

Gastric duplications are most often found on the greater curvature and usually do not communicate with the stomach.[2] A carcinoma has been found in an adult gastric duplication.[15]

Because of their location, gastric duplications can usually be excised by a limited partial gastrectomy. Unusual locations may necessitate more complete gastric resection. Duodenal duplications often lie behind the duodenum and usually do not communicate with the bowel lumen.[13] The first reported surgical procedure for duodenal duplication was that of excising the common wall so that the duplication opened into the duodenum.[8] Cystoenterostomy by the Roux-Y technique has been reported with satisfactory results in some cases.[13] Occasionally, extraluminal excision of duodenal duplications is possible.

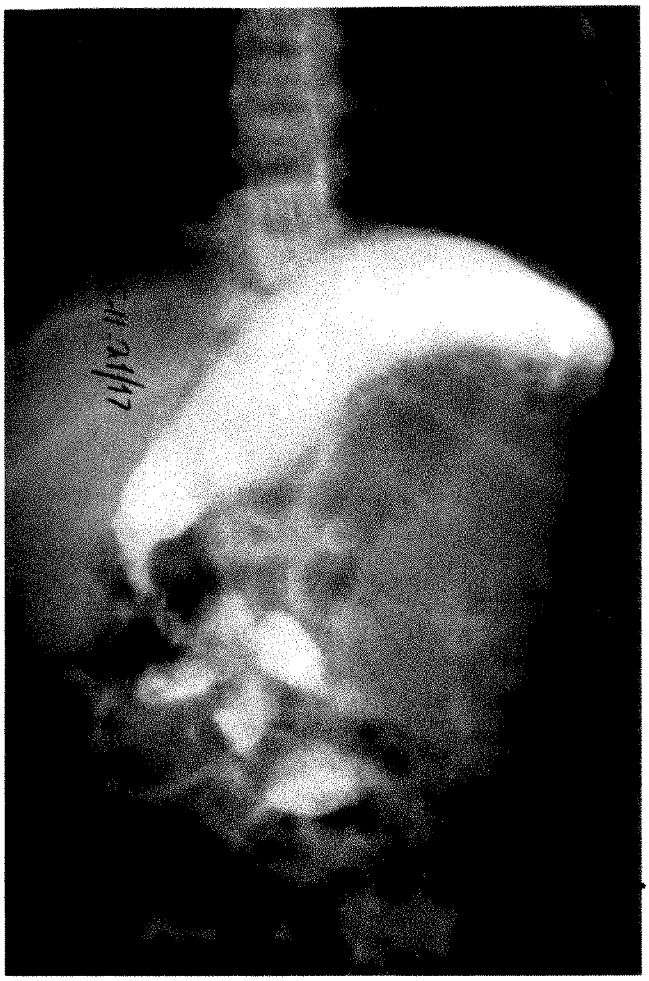

FIG. 3. Large gastric duplication on greater curvature.

TABLE 3. *Small Bowel Duplications*

Patients	Age	Size (cm)	Clinical Presentation	Location	Ectopic Mucosa	Result
1.	3 mos	1	none (autopsy)	Ileum	—	Died: congenital heart disease
2.	2 mos	1	none (autopsy)	Ileum		Autopsy finding
3.	5 mos	20*	B	Jejunum	Gastric	Resection; recovery
4.	4 mos	3	M, I	Ileum	—	Died postop
5.	13 yrs	12, 9, 4	O, B, V	Ileum × 3	—	Resection; recovery
6.	2 mos	8 × 7	O, M	Ileum	—	Resection; recovery
7.	4 mos	1.2	I	Ileum	—	Resection; recovery
8.	2 yrs	2	O	Ileum	—	Resection; recovery
9.	1 day	5 × 4	O	Ileum[a]	—	Resection; recovery
10.	7 days	4	O, M, B	Ileum	—	Resection; recovery
11.	4 days	2	O	Ileocecal	Colonic	Resection; recovery
12.	21 mos	5	I, M	Ileocecal	Colonic	Resection; recovery
13.	2 wks	2.5	B	Ileocecal	Colonic	Resection; recovery
14.	11 mos	2	O	Ileocecal	Colonic	Resection; recovery
15.	1 day	3.5	O, M	Ileum	—	Died; sepsis, volvulus
16.	2 mos	2.5	O, I	Ileum	—	Resection; recovery
17.	1 day	15*	O	Ileum	Gastric	Died; anastomotic leak
18.	1 day	1	O, M	Jejunum[a]	—	Died; respiratory failure
19.	5 wks	4	O	Ileum	—	Resection; recovery
20.	4 days	3	none (autopsy)	Ileum	—	Died after TEF repair
21.	2 days	10	none (autopsy)	Jejunal[v]	—	Died after omphalocele
22.	10 mos	16*	B	Jejunal[t,v]	Gastric	Resection; recovery
23.	11 mos	3	O	Ileal[a]	—	Died; sepsis
24.	6 wks	7 × 5	M	Ileal	—	Resection; recovery
25.	8 mos	10 × 7	M	Jejunum	—	Resection; recovery
26.	5 mos	5	M	Ileum	—	Resection; recovery
27.	3 wks	15*	M	Ileum	—	Resection; recovery
28.	8 mos	2.5	M	Jejunum[t]	Gastric	Resection; recovery
29.	18 mos	7*	B	Ileum	Gastric	Resection; recovery
30.	2 days	4	O	Ileum[a]	—	Died postop
31.	5 days	3, 2	O, M	Ileum × 2	—	Resection; recovery

* tubular
O — obstruction
M — mass
B — bleeding
I — intussusception
V — volvulus
a — atresias
t — thoracic duplication also
v — vertebral defects

Of the six gastric duplications (in five patients) in this series, one was an incidental finding at autopsy, one was found at autopsy and was the cause of death (perforation), and three patients are doing well following resection, one having two duplications. The one pyloric duplication had a satisfactory result from the type of excision described by Grosfeld.[9] Two duodenal duplications were found incidentally in the child who died from a perforated gastric duplication. One duodenal duplication patient died shortly after attempted resection, and the other patient had a cysto-Roux-Y enterostomy and is doing well nine years later.

Small Bowel

The ileum is the most common location for duplications of the alimentary tract. These are located on the mesenteric border and have a common blood supply with the adjacent small bowel. The duplications may be spherical or tubular. Approximately 50% of patients in this series had small bowel duplications. Two cases had multiple lesions (Table 3). Six duplications occurred in the jejunum and 28 were found in the ileum or ileo-cecal area (Fig. 4). Five lesions were tubular (6.8–20 cm in length); the remainder were spherical (1–12 cm). Five of the duplications contained ectopic gastric mucosa and three of these presented with bleeding. A preoperative diagnosis of small bowel duplication has been made in some cases by use of the technetium scan.[20] In addition to blood loss, the clinical findings in this group included obstruction in 15 cases and a palpable abdominal mass in 12 cases. Coexistent intestinal atresias were present in four cases and a vascular etiology for such duplications has been proposed by Favara.[5]

Spherical duplications usually require a segmental resection of the duplication and the adjacent small bowel. Occasionally, long tubular duplications would require resection of too much normal small bowel; in this situation, the distal portion of the tubular duplication can be opened into the normal lumen with the duplication being left in place.

Twenty-one of the 31 patients had resection of their duplication without problems. Four patients had an asymptomatic duplication discovered at autopsy.

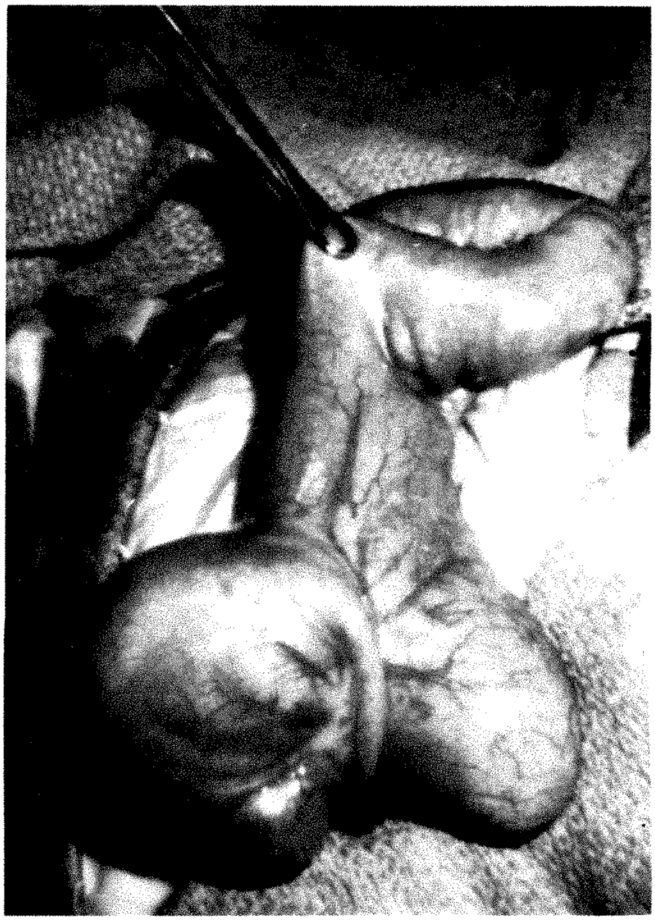

FIG. 4. Cystic duplication in mesentery near ileo-cecal valve.

There were six deaths in this group, two of the deaths resulting from complications of the multiple atresias that were associated with the duplication. One death was caused by agenesis of the lung and respiratory failure, and one death was the result of volvulus with extensive gangrene of the small bowel. Two final patients died directly as a result of complications related to resection of the duplication.

Appendix, Colon and Rectum

Fourteen duplications of the appendix, colon or rectum were found in this review (Table 4). Three (#9, #10, #12) were discovered incidentally at autopsy, three presented because of obstruction (#1, #2, #3) and the remainder were discovered by the presence of a rectal or abdominal mass.

Of the 14 patients with hindgut duplications, bladder anomalies were present in the two patients (#4, #5) who had duplicated appendices, and three had total colonic duplication with genitourinary anomalies (Fig. 5). One of the appendiceal patients is alive and well after duplication resection numerous procedures to reconstruct the urinary tract, while the other one died postoperatively from aspiration. One of the colonic patients (#3) did well after the two lumens were joined distally as suggested by Soper.[19] Another (#1) was cured by partial colon resection only to die of congenital heart disease six months later; the third (#2) died in 1944 of "megacolon" without operation.

Many comments have been made concerning the relationship between duplications of the hindgut and genitourinary anomalies. Although any hindgut duplication may have related genitourinary anomalies, the tubular duplications of the entire colon are the type most commonly found to have double bladders, double urethras or double external genitalia.[19] Ravitch concluded that these associations occur as a result of partial twinning.[17]

Total colonic duplications, which communicate proximally but not distally, are best treated by distal fenestration. Because of the frequency of associated urinary anomalies in this type, appropriate evaluation of the genitourinary tract is indicated preoperatively. Cystic duplications of the colon are handled by partial colectomy; this was done in our three symptomatic cases with one death from sepsis, the two additional cases being incidental autopsy findings. Rectal duplications may be totally resected or the common rectal-duplication wall removed, one of our patients was so treated successfully and the other had his duplication as an unexpected autopsy finding. The two retroperitoneal duplications were treated by excision with uneventful recoveries in both instances.

Colonic duplications occasionally have ectopic gastric mucosa; peptic ulceration therefore is a potential complication. Another theoretical risk of any

TABLE 4. *Appendix, Colon, Rectum*

Patients	Age	Size (cm)	Clinical Feature	Location	GU or Vertebral Anomaly	Result
1.	18 mos	Total colon + appendix + ileum 6	Obstruction Rectal bleeding	Anti-mesenteric	Extrophy of bladder Meningomyelocele	Died 6 mos. postop; truncus arteriosus
2.	8 mos	Total colon + appendix	Obstruction	Anti-mesenteric	Double bladder	Died without surgery (1944)
3.	14 yrs	Total colon + appendix	Constipation	Anti-mesenteric	Double bladder Hemivertebra	Distal fenestration; recovered
4.	1 mo	Double appendix	—		Double bladder Urethra & penis Hemivertebra	Doing well after multiple procedures for other anomalies
5.	1 mo	Double appendix	—		Cloacal extrophy Meningomyelocele	Died of aspiration
6.	2 wks	17 × 4	Obstruction Mass	Transverse colon		Resection; recovered
7.	3 mos	4 × 3	Mass	Cecum	—	Died of sepsis
8.	7 yrs	4	Mass	Cecum	—	Right colectomy; recovered
9.	3 days	3	None (autopsy)	Transverse colon	—	Incidental at autopsy
10.	7 mos	1	None (autopsy)	Hepatic flexure	—	Incident at autopsy
11.	6 yrs	5	Obstipation Mass	Rectum	Hemivertebra	Excision; recovered
12.	1 day	5 × 3	None (autopsy)	Rectum	—	Died of congenital heart disease
13.	3 mos	8	Mass	Left flank Retroperitoneal	—	Excision; recovered
14.	4 mos	10	Mass	Left flank Retroperitoneal	—	Excision; recovered

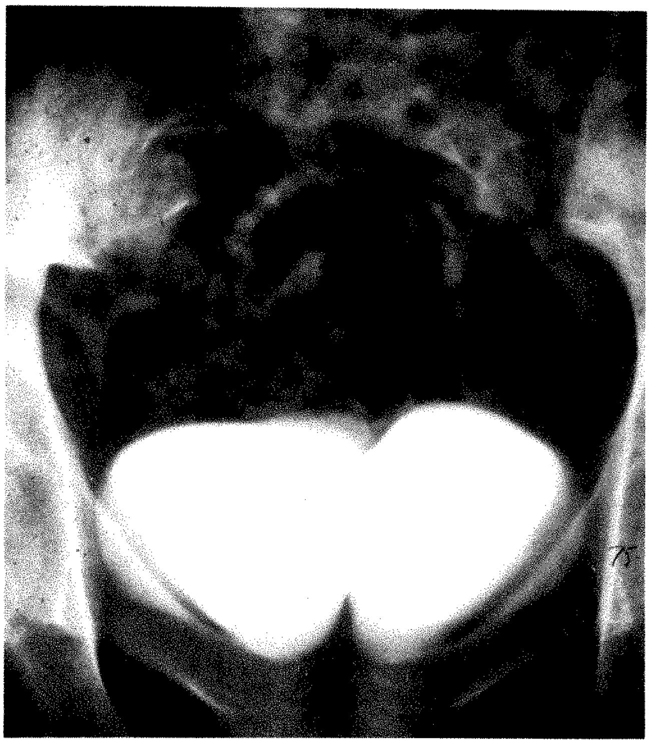

FIG. 5. Cystogram in 15-year-old with total colonic duplication and septate bladder.

procedure which leaves a portion of a duplication in place is the malignant potential as reported by Orr and Edwards.[15]

Summary

Duplications of the alimentary tract are relatively rare. They usually become symptomatic early in life. The symptoms depend on the location of the lesion and the type of mucosal lining. Peptic complications may occur when ectopic gastric mucosa is present. The cause of duplication formation is unknown, but the results of surgical therapy are good except for the patients who have other anomalies which in themselves carry a high morbidity and mortality.

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Treatment of Caustic Injuries of the Esophagus:

A Ten Year Experience

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The methods of managing 32 patients sustaining caustic injuries to the esophagus are assessed. Treatment of these patients must be individualized according to the type of caustic ingested, the degree of burn and other clinical signs. While an aggressive approach is favored for second and third-degree burns in the form of early esophagogastrectomy with subsequent colon interposition, operation is not necessary in all patients, particularly those with first-degree burns. The use of antibiotics is recommended as soon as the diagnosis of esophageal injury is established. The efficacy of steroids in preventing stricture formation, especially with third-degree burns, is questioned.

In the past ten years lye in a crystalline or liquid state has been marketed commercially as a drain cleaner and become widely available. It is frequently ingested either accidentally or with the intent of doing self-injury. Since such ingestion of lye may result in immediate and permanent injury to the lips, mouth, larynx, esophagus and stomach, it is imperative that the physician promptly determine the extent and severity of the injury and institute the appropriate therapy. Early in our experience these patients were treated in the conventional manner (steroids, antibiotics, early dilatation) with disastrous results. Consequently, an aggressive approach in the form of early esophagogastrectomy was recommended for all patients who ingested these corrosives.[1,7,8]

Since that time the Federal Hazardous Substance Act has modified the concentration of these corrosives so that the earlier recommended therapy has been altered. Over the past ten years we have treated 32 patients who have ingested highly alkaline caustics. This report assesses our methods of handling patients who have sustained caustic injuries to the esophagus and stomach and discusses our present plan of management.

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Management

All patients with physical findings of caustic ingestion must be admitted to the hospital; in fact, anyone in whom there is the least suspicion of caustic ingestion should be admitted and undergo evaluation. An attempt should be made to find the container that held the ingested caustic or some of the material inself for proper identification.

In those patients who are hypotensive on admission, arterial and central venous catheters are inserted for constant pressure monitoring. Hypovolemia is treated with either whole blood or colloid-containing fluids. The patient is carefully observed for airway obstruction. Laryngeal edema is frequently seen in the first 24 hours in association with severe caustic burns of the esophagus, and endotracheal intubation or tracheostomy may be needed. In view of the instantaneous nature of the injury produced by liquid caustics, water or other liquids to "dilute the caustic" are of little value. In fact, they may produce additional vomiting or retching that may aggravate the situation. For the same reason, emetics and gastric lavage are contraindicated.

The patient is kept NPO and maintained on intravenous fluid. Clear fluids are begun by mouth only when the patient is able to swallow his saliva; he may then progress to a regular diet as tolerated. If the patient is unable to swallow, a gastrostomy should be performed.

Antibiotics are administered as soon as the diagnosis of esophageal injury is established. Our preference is for ampicillin (40 mg/kg/body weight/day in divided doses) because it is effective against oropharyngeal flora. It should be administered intravenously at first

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Submitted for publication: April 18, 1977.

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and then intramuscularly until oral feedings are begun. The antibiotics are discontinued at seven days if the patient is afebrile. If after a two week course of antibiotic therapy fever continues, one should suspect an associated complication such as mediastinitis, peritonitis, or a localized abscess in either the mediastinum or peritoneum.

Contrast visualization of the esophagus and stomach is carried out shortly after admission. Esophagoscopy is done upon admission or not later than 24 hours after the ingestion. The esophagoscope is inserted only as far as the first identifiable mucosal lesion and not beyond. This safeguards against esophageal perforation. Those patients in whom there are no oropharyngeal or esophageal burns and in whom the barium swallow is normal are discharged after 24 hours of observation. A repeat barium swallow is performed at regular intervals for a year so that an unrecognized esophageal stricture will not be overlooked.

Liquid Caustics

The liquid caustics, because of their high specific gravity, pass rapidly through the esophagus and reach the stomach soon after ingestion, destroying its full thickness and even adjacent tissues and causing gastric perforation. Severe esophageal injury occurs frequently.

A nasogastric tube is inserted cautiously and the stomach is aspirated. If the aspirate is basic and the alkalinity does not cease with gentle and limited irrigation, it is presumed that the stomach and esophagus are burned. Contrast visualization of the esophagus and stomach is also obtained. Esophagoscopy is not performed in this circumstance, as it does not give accurate information about the extent of necrosis. Instead a celiotomy is performed, and if the gastric wall is ecchymotic or black, indicating a necrotic stomach, a gastrectomy is performed. At times a burn extends through the stomach wall to involve the adjacent viscera such as colon, pancreas, spleen, or small bowel. If damaged, these structures are also removed.

It has now been amply demonstrated that when the stomach is necrotic following caustic ingestion, the esophagus will also be necrotic or so severely burned that a nondilatable stricture will develop within several months.[3] Therefore, a right thoracotomy is performed, and if the esophagus is necrotic, total esophagostomy and left cervical esophagostomy should be carried out. Colon interposition is performed three or four weeks later. If the distal intra-abdominal segment of esophagus is necrotic or if contrast examination shows dilation of the esophagus with retention of either swallowed air or contrast material (which implies diffuse muscular necrosis and impending perforation), esophagectomy and left cervical esophagostomy are performed. If neither of these abnormalities is present, the extent and severity of the esophageal injuries are assessed by careful esophagoscopy and managed conservatively with antibiotics and later dilations.

If the gastric aspirate is acidic and peritoneal signs are present, a ceilotomy is performed and gastrectomy, esophagostomy, or both carried out if indicated. When the gastric aspirate is acidic (as is apt to occur when ingestion occurs on a full stomach) and there are no peritoneal signs, there is little likelihood that the stomach is seriously burned, and a celiotomy is not performed. An esophagectomy is now recommended only if there are clinical signs of perforation or if a contrast examination shows evidence of impending perforation. When neither is present, an esophagoscopy is performed to assess the severity and extent of the injury.

Solid-state Caustics

As a rule, the ingestion of caustic crystals almost immediately produces severe pain that causes the patient to stop further ingestion. The crystals tend to adhere to the mucous membranes of the tissues with which they first come into contact, namely, the mouth, pharynx, and esophagus. The majority of patients who have ingested crystals do not suffer severe esophageal burns. Those patients who sustain a second or third-degree burn often develop an esophageal stricture. Dilatation is not started until healing is complete and epithelialization of the mucosa is seen as far as the esophagoscope can be advanced. This usually takes four to five weeks. Dilatation is carried out with the mercury-filled, tapered Hurst-Maloney bougies. If a gastrostomy has been performed, a retrograde esophageal dilator with the Tucker bougie is an alternate method of dilatation. Even if dilatation is delayed until healing has occurred, there is still an increased risk of perforation, hemorrhage, or both when it is instituted. Therefore dilatation should be carried out as carefully as possible. If bleeding occurs, dilation should be temporarily discontinued until it has stopped; dilation is then reinstituted cautiously.

Clinical Findings

Over the past ten years 32 children and adults were treated for caustic injuries to the esophagus and stomach. The age and sex of the patients are listed in Table 1. The caustic ingested and its state at time of

TABLE 1. *Age and Sex of Patients*

Age (year)	Male	Female
<-1	3	3
1-5	10	3
5-20	1	2
20-40	2	4
>-40	4	0

ingestion are listed in Table 2. Since the pathophysiology and treatment of burns caused by solid or liquid agents are different they will be discussed separately.

Results (Tables 4 and 5)

Liquid Caustic

In only five of the 18 patients ingesting a liquid caustic no oropharyngeal abnormalities were noted on the initial or subsequent examination. In other patients oropharyngeal lesions ranged from scattered areas of superficial mucosal erosions of the lips and tongue in six patients to deep and extensive destruction of the lingual, buccal and pharyngeal mucosa in seven patients. Table 3 summarizes the findings at esophagoscopy. A first-degree burn was characterized by superficial mucosal hyperemia, mucosal edema and superficial sloughing. A second-degree burn involved all layers of the esophagus and was characterized by exudate, ulceration and loss of mucosa. A third-degree burn was one which, in addition to involving the esophageal wall, had eroded through the esophagus into the periesophageal tissues. There was only one perforation associated with the initial esophagoscopy.

Three patients with third-degree burns of the esophagus underwent an emergency esophagogastrectomy as their initial mode of therapy within 12 hours following the ingestion. There were no deaths among these patients. Following this a colon interposition was performed from three weeks to six months later. There were no deaths and only one anastomotic leak.

In contrast to this there were 11 patients with second or third-degree burns of esophagus who did not undergo esophagogastrectomy initially. Four of these patients were treated with steroids, antibiotics and early dilatations. Despite the fact that the perforations were recognized early, three of these patients died, two from overwhelming sepsis and one from an aortoesophageal fistula. An additional patient was perforated during dilatation and was treated by drainage alone. He has subsequently been lost to follow-up. The remaining seven patients were treated with antibiotics and late dilatation. All of these patients developed severe esophageal strictures which necessitated colon interposition in six patients.

TABLE 2. *Caustic Ingested and Its State at Time of Ingestion*

Liquid state	18
Liquid Plumer	9
Draino	5
Lye	3
Plunge	1
Solid State	14
Draino	12
Rooto	2

TABLE 3. *Summary of Esophoscope Examination*

	Liquid	Solid
First-degree	4	7
Second-degree	3	4
Third-degree	11	3

There were four patients who sustained only first-degree esophageal burns. There were no deaths in this group of patients and none required an emergency esophagogastrectomy. Two of these patients developed an esophageal stricture which was easily treated by esophageal dilatation.

Solid-state Caustic (14 patients)

In 12 of the patients with solid-state caustic there were oropharyngeal abnormalities noted on the initial examination. In six patients there was extensive destruction of the lingual, buccal and pharyngeal mucosa in addition to burns of the face. In six patients there were only superficial mucosal erosion of the lips and mouth and in two patients there were no oropharyngeal abnormalities noted on the initial examination. Table 3 summarizes the findings at esophagoscopy. There were eight patients who sustained only first-degree burns. None of these patients developed an esophageal stricture. Four of the six patients with second or third-degree burns were treated with

TABLE 4. *Results with Liquid Ingestion*

Second and third-degree burns	14
Immediate Esophagogastrectomy	3
Early dilatation, steroids	4
death	3*
perforation	1
Antibiotics alone + dilatation	7
nondilatable stricture	7
colon interposition	6†
First-degree Burn	4
Dilatable stricture	2
No stricture	2
Death	0

* One death secondary to esophageal perforation.
† Patient requires colon interposition but refused operation.

TABLE 5. *Results with Solid-State Caustic*

Second and Third-degree Burns	6
Early dilatation	4
death	1
perforation	3
Nondilatable stricture (colon interposition)	1
Dilatable stricture	1
First-degree Burns	8
Deaths	0
Stricture	0

early dilatation. One of these patients died as a result of a trachea-innominate fistula. In the remaining three patients perforation of the esophagus occurred which necessitated an emergency esophagogastrectomy in two patients. One of the two remaining patients with second and third-degree esophageal burns developed a nondilatable stricture which necessitated a colon interposition.

Discussion

Our discussion concerns only the principles of management. The pathology, pathophysiology, clinical and radiographic features have been described elsewhere.[3]

Early in our experience patients with caustic injuries of the esophagus were treated with steroids, antibiotics and early dilatations. The basis for steroid therapy in the treatment of caustic injuries of the esophagus is the observation by Spain and associates that early administration of cortisone in mice inhibited fibroplasia and formation of granulation tissue.[10] They also observed that, to be effective, glucocorticoids must be given within 48 hours of injury. Similar findings showing that steroids inhibit the formation of strictures after caustic ingestion in animals have been reported by Wieskuff,[11] Haller and colleagues,[2] and others.[9] These experimental studies have been supported by Haller's[2] report on 60 patients ,with esophageal burns after caustic ingestion. Stricture developed in 25% of the patients treated without steroids compared with only nine per cent of those treated with steroids plus antibiotics. Contrasting results have been reported by Middlekamp, Ashcraft, and Leape.[4-6] In these series 18 of 19 patients with a severe (third-degree) circumferential esophageal burn developed a stricture despite the early administration of steroids and antibiotics. In addition, an increased occurrence of perforation has been found when steroids were used following ingestion of concentrated solutions of alkali. Similar results were found in our patients who were treated with steroids. Steroids have also been found to mask symptoms of infection in other mediastinal structures and have delayed healing.
As a result of these studies and our own
the efficacy of steroids in preventing stric
tion after caustic ingestion is "highly que
especially with third-degree burns. Becaus
tentially serious complications that might
their administration and the fact that their
tion does not prevent stricture formation
degree burns, it is our conviction th
should not be used in the treatment of
injuries caused by liquid caustics.

In addition, early dilatation was associa
increased incidence of perforation. Five o
tients treated with early dilatation develope
tion of the esophagus. Consequently, an
approach in the form of early esophagog
was recommended for all patients who ing
corrosives. As our experience increased in t
ment of these patients it soon became ap
not all patients who had ingested the
agents required an esophagogastrectomy.
of the esophagus following solid-state caust
was an infrequent occurrence, whereas pe
the esophagus following liquid caustic ing
common. The indications for esophagog
have been discussed in detail in the section
ment.

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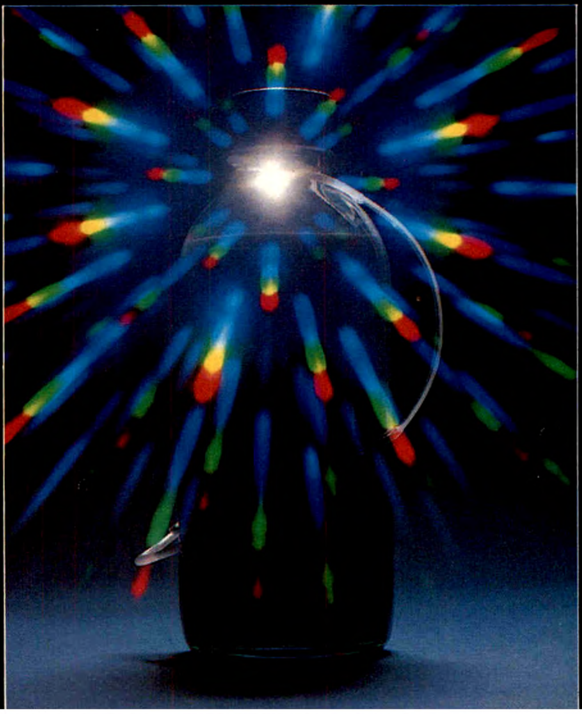
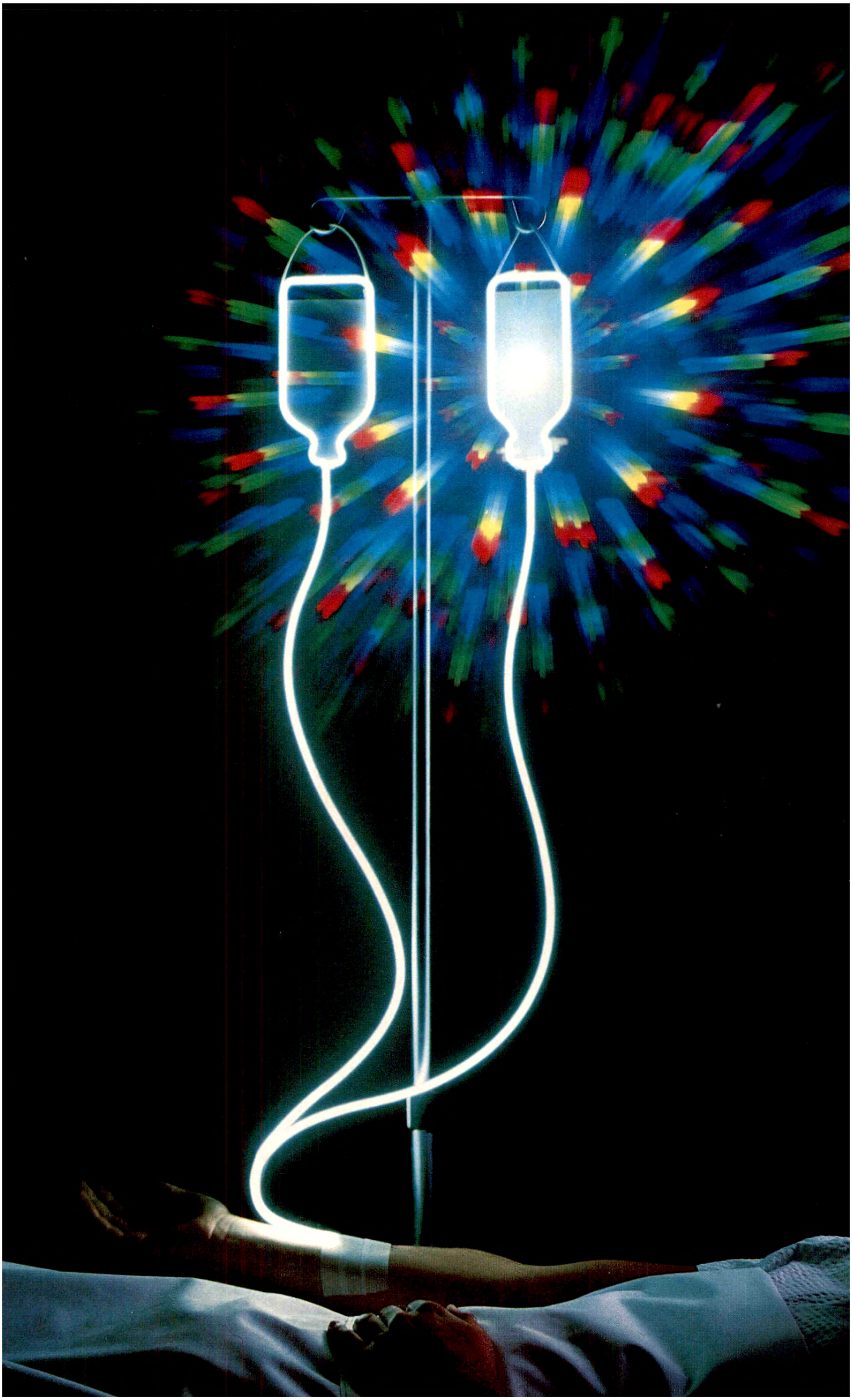
Total parenteral nutrition.

Now possible via peripheral vein





Intralipid® 10% I.V. Fat Emulsion

Before the availability of Intralipid 10% I.V. Fat Emulsion, hyperalimentation was the only method of administering highly concentrated solutions of calories and nutrients. But hyperalimentation requires central venous catheterization, with all its attendant risks.

Now, with Intralipid 10% I.V. Fat Emulsion, there is an alternative — the lipid system of total parenteral nutrition. The lipid system consists of Intralipid 10% I.V. Fat Emulsion in conjunction with glucose, amino acids, electrolytes, minerals and vitamins, and provides all essential nutrients, including fat*, and adequate calories, via peripheral vein.

Intralipid 10% I.V. Fat Emulsion is a highly concentrated source of calories, providing 1.1 Calories per ml in an isotonic solution.

And because the lipid system includes fat in the I.V. nutritional regimen, Intralipid 10% I.V. Fat Emulsion attains the goal of balanced I.V. nutrition and prevents or corrects the symptoms of essential fatty acid deficiency.

Intralipid 10% I.V. Fat Emulsion also allows for balanced I.V. nutrition via central vein in those patients who require larger amounts of calories than can be supplied by peripheral infusion, or who have peripheral veins unsuitable for parenteral feeding. Central vein infusion of Intralipid 10% I.V. Fat Emulsion, with other nutrients infused separately can decrease the risk of metabolic disorders often encountered with hyperalimentation infusions — including osmotic diuresis, hyperglycemia, rebound hypoglycemia, hyperosmolar non-ketotic dehydration — and prevents or corrects essential fatty acid deficiency.

Intralipid 10% I.V. Fat Emulsion — could make the lipid system your method of choice in I.V. nutrition.

Now possible. Total parenteral nutrition via peripheral vein.

See following page for full prescribing information.

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*Intralipid 10% I.V. Fat Emulsion must not be mixed with electrolyte or other nutrient solutions in order to avoid disturbing the stability of the emulsion. Filters must not be used with Intralipid 10% I.V. Fat Emulsion.

Intralipid® 10% I.V. Fat Emulsion

DESCRIPTION

Intralipid® 10% (10% Intravenous Fat Emulsion) is a fat emulsion prepared for intravenous administration. It is made up of 10% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and Water for Injection. In addition, Sodium Hydroxide has been added to adjust the pH to between 5.5 and 9.0.

The soybean oil is a refined natural product consisting of a mixture of neutral triglycerides of predominantly unsaturated fatty acids. The major component fatty acids are linoleic (54%), oleic (26%), palmitic (9%) and linolenic (8%).

Intralipid® 10% (10% Intravenous Fat Emulsion) has an osmolarity of approximately 280mOsm/liter and contains emulsified fat particles of approximately 0.5 micron size.

The total caloric value, including fat, phospholipid and glycerol, is 1.1 calories per ml. of Intralipid® 10% (10% Intravenous Fat Emulsion).

ACTIONS

Intralipid® 10% (10% Intravenous Fat Emulsion) is metabolized and utilized as a source of energy causing an increase in heat production, decrease in respiratory quotient and increase in oxygen consumption following its administration. The infused fat particles are cleared from the blood stream in a manner thought to be comparable to the clearing of chylomicrons.

Intralipid® 10% (10% Intravenous Fat Emulsion) will prevent the biochemical lesions of essential fatty acid deficiency (EFAD), and correct the clinical manifestations of the EFAD syndrome.

INDICATIONS

Intralipid® 10% (10% Intravenous Fat Emulsion) is indicated as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than five days) and as a source of essential fatty acids when a deficiency occurs.

CONTRAINDICATIONS

The administration of Intralipid® 10% (10% Intravenous Fat Emulsion) is contraindicated in patients with a disturbance of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis and acute pancreatitis if accompanied by hyperlipemia.

Intralipid® 10% (10% Intravenous Fat Emulsion) must not be mixed with electrolyte or other nutrient solutions; no additives can be placed in the bottle of Intralipid® 10%. It is supplied in single dose containers; a partly used bottle must not be stored for later use.

Filters should not be used with Intralipid® 10% (10% Intravenous Fat Emulsion).

Do not use any bottle in which there appears to be an oiling out of the emulsion.

WARNINGS

Caution should be exercised in administering Intralipid® 10% (10% Intravenous Fat Emulsion) to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders, or when there is danger of fat embolism.

PRECAUTIONS

When Intralipid® 10% (10% Intravenous Fat Emulsion) is administered, the patient's capacity to eliminate the infused fat from the circulation must be monitored. The lipemia must clear between daily infusions.

During long term intravenous nutrition with Intralipid® 10% (10% Intravenous Fat Emulsion), liver function tests should be performed; and if these tests indicate that liver function is impaired, the therapy should be withdrawn.

Frequent (some advise daily) platelet counts should be done in neonatal patients receiving parenteral nutrition with Intralipid® 10% (10% Intravenous Fat Emulsion).

Cutter Medical
Division of Cutter Laboratories, Inc.
Berkeley, California 94710

ADVERSE REACTIONS

The adverse reactions observed can be separated into two classes:

1. Those more frequently encountered which are due either to contamination of the intravenous catheter and result in sepsis, or to vein irritation by concurrently infused hypertonic solutions and may result in thrombophlebitis. These adverse reactions are inseparable from the hyperalimentation procedure with or without Intralipid® 10% (10% Intravenous Fat Emulsion); and
2. Those less frequent reactions more directly related to Intralipid® 10% (10% Intravenous Fat Emulsion) which are: a) **immediate or early adverse reactions,** each of which has been reported to occur, in clinical trials, in an incidence of less than 1%: dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness and irritation at the site of infusion, and rarely thrombocytopenia in neonates. b) **delayed adverse reactions:** hepatomegaly, splenomegaly, thrombocytopenia, leucopenia, transient increases in liver function tests, and over loading syndrome (focal seizures, fever, leukocytosis, splenomegaly and shock).

The deposition of a brown pigmentation in the reticuloendothelial system, the so-called "intravenous fat pigment", has been reported in patients infused with Intralipid® 10% (10% Intravenous Fat Emulsion). The cause and significance of this phenomenon are unknown.

DOSAGE AND ADMINISTRATION

Intralipid® 10% (10% Intravenous Fat Emulsion) should be administered as a part of total parenteral nutrition intravenously via a peripheral vein or by central venous infusion.

Adult Patients The initial rate of infusion in adults should be one ml./minute for the first 15 to 30 minutes of infusion. If no untoward reactions occur (see Adverse Reactions section), the infusion rate can be increased so that 500 ml. will be infused over a period of four hours. Only 500 ml. of Intralipid® 10% (10% Intravenous Fat Emulsion) should be infused into adults on the first day of therapy. If the patient has no untoward reactions, the dose can be increased on the following day. The daily dosage should not exceed 2.5 g./kg. of body weight. Intralipid® 10% should make up no more than 60% of the total caloric input of the p
tient. Carbohydrate and a source of amino aci
should comprise the remaining 40% or more
the caloric input.

Pediatric Patients The initial rate of infusion
pediatric patients should be 0.1 ml./minute f
the first 10 to 15 minutes. If no untoward reactio
occur, the rate can be increased to permit in
sion of 1 g./kg. in four hours. The daily dosag
should not exceed 4 g./kg. of body weight.
tralipid® 10% (10% Intravenous Fat Emulsio
should make up no more than 60% of total calor
input of the patient. Carbohydrate and a sour
of amino acids should comprise the remaini
40% or more of the caloric input.

Fatty Acid Deficiency When Intralipid® 10% (1
Intravenous Fat Emulsion) is administered to c
rect fatty acid deficiency, eight to ten percent
the caloric input should be supplied by
tralipid® 10% in order to provide an adequ
amount of linoleic acid to correct the deficien

Administration Intralipid® 10% (10% Intraven
Fat Emulsion) should be infused separately fr
any other intravenously administered solutions
order to avoid disturbing the stability of the em
sion. It must not be mixed with electrolyte
other nutrient solutions, and drugs or vitami
must not be added to the emulsion in the infusi
bottle. It can be infused into the same peripher
vein as the carbohydrate-amino acids soluti
by means of a Y-connector located near the in
sion site, and flow rates of each solution shou
be controlled separately by infusion pumps. Filte
should not be used with Intralipid® 10% emulsi

A special Intralipid® 10% (10% Intravenous F
Emulsion) intravenous administration set
available.

Intralipid® 10% (10% Intravenous Fat Emulsio
is supplied in single dose containers; the rema
ing contents of a partly used bottle must not
stored for later use.

STORAGE

Intralipid® 10% should be stored under refr
eration at 4° to 8° C.

Do not freeze Intralipid® 10% (10% Intraven
Fat Emulsion); if accidentally frozen, discard bo

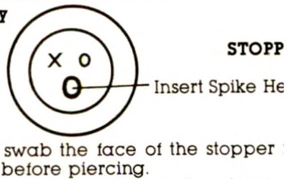
HOW SUPPLIED

Intralipid® 10% (10% Intravenous Fat Emulsio
is supplied as a sterile emulsion in 500
containers.

IMPORTANT
ADDITIONAL PRODUCT INFORMATION

Read Carefully Before Administration of Intralipid® I.V. Fat Emulsion

1. Stopper Entry



a. Be sure to swab the face of the stopper
mediately before piercing.
b. Insert spike through the largest circle of p
pared stopper with a straight thrust and th
twist to fully seat spike.

**2. Special Intralipid® I.V. Fat Emulsion Adm
istration Set**

A special Intralipid® I.V. Fat Emulsion adminis
tion set is provided with each bottle. Conv
tional administration sets contain polyvi
chloride (PVC) components that contain DE
(Diethyl Hexyl Phthlate) as a plasticizer. Fat c
taining fluids such as Intralipid® extract DE
from these PVC components.

The special Intralipid® I.V. Fat Emulsion set d
not contain DEHP. Therefore, this special
should be used for the administration of
tralipid® 10% (Intravenous Fat Emulsion).

Books Received for Review—April-June 1978

Lecture Notes on Urology. Second edition. John Blandy. 320 pp. Philadelphia, J. B. Lippincott Company, 1978. $17.50.

Plastic and Reconstructive Surgery of the Face and Neck. Vol. I: Aesthetic Surgery. Vol. II: Rehabilitative Surgery. by G. A. Sisson & M. E. Tardy, Jr. (eds.) Vol. I 236 pp., Vol. II 348 pp. New York, Grune & Stratton, Inc., 1977.

Renal Pathology in Biopsy. H. U. Zollinger and M. J. Mihatsch. 684 pp., New York, Springer-Verlag, 1978. $85.00.

Postcholecystectomy Syndromes: A Clinical Approach to Etiology, Diagnosis, and Management. By C. J. Schein. 264 pp., Hagerstown, Harper & Row, Publishers, Inc., 1978. $25.00.

Pathology of the Lung. Third edition. H. Spencer. 1099 pp. Philadelphia, W. B. Saunders Company, 1977.

Coronary Artery Surgery. J. L. Ochsner and N. L. Mills. 275 pp. Philadelphia, Lea & Febiger, 1978. $25.00.

Surgical Pediatric Urology. H. B. Eckstein, R. Hohenfellner and D. I. Williams. 533 pp. Philadelphia, W. B. Saunders Company, 1978. $110.00.

Genitourinary Problems in Women. J. R. Robertson. 150 pp. Springfield, Charles C Thomas, 1978. $16.75.

Recent Advances in Intensive Therapy. I. Ledingham. 257 pp. New York, Churchill Livingstone, 1978. $23.00.

Topics in Gastroenterology. Fifth edition. S. C. Truelove & E. Lee (eds.). 349 pp. Philadelphia, J. B. Lippincott Company, 1978. $39.50.

Aspiration Cytology of the Breast. H. Schondorf. 141 pp. Philadelphia, W. B. Saunders Company, 1978. $27.50.

Malignant Hyperthermia. J. A. Aldrete and B. A. Britt (eds.). 560 pp. New York, Grune & Stratton, Inc., 1978. $25.50.

Interpretation of Diagnostic Tests. J. Wallach. 639 pp. Boston, Little, Brown and Co., 1978. $9.95.

Pharmacology: Drug Actions and Reactions. R. R. Levine. 513 pp. Boston: Little, Brown and Co., 1978. $11.50.

AAOS: Symposium on Reconstructive Surgery of the Knee. 365 pp. St. Louis, C. V. Mosby Company, 1978. $39.50.

Cranitomography: An Atlas and Guide. Klaus Reisner and Jochen Gosepath. 196 pp. Littleton, Thieme-PSG Publishing Company, Inc., 1977.

Surgical Endocrinology: Clinical Syndromes. S. R. Friesen. 430 pp. Philadelphia, J. B. Lippincott Company, 1978. $27.00.

Clinical Anesthesia Procedures of the Massachusetts General Hospital. P. W. Lebowitz. 437 pp. Boston, Little, Brown & Co. 1978. $10.95.

Hodgkin's Disease and the Lymphatics, Vol. II 1977. C. R. Taylor. 400 pp. Montreal, Eden Press, 1978.

Recent Results in Cancer Research Tactics and Strategy in Cancer Treatment. G. Mathe (ed.). 220 pp. New York, Springer-Verlag, 1978. $29.80.

Cancers et Grossesse. D. Querleu, P. Cappelaere, G. Crepin and A. Demaille. 372 pp. Paris, Masson, 1978.

Les Voies d'Acces Vasculaires en Vue d'Hemodialyse. V. di Marino. 249 pp. Paris, Masson, 1978.

Gross Anatomy Dissector: A Companion for the Atlas of Clinical Anatomy. By R. S. Snell. 356 pp. Boston, Little, Brown & Co. $9.95.

Venous Problems. J. J. Bergan and J. S. T. Yao. 613 pp. Chicago, Year Book Medical Publishers, 1978. $29.95.

Nephrolithiasis-Pathogenesis and Treatment. F. L. Coe. 235 pp. Chicago, Year Book Medical Publishers, 1978. $25.95.

Clinical Pharmacology: Basic Principles in Therapeutics. Second edition. K. L. Melmon and H. F. Morrelli. 1146 pp. New York, Macmilliam, 1978. $25.00.

General Surgical Operations. R. M. Kirk (ed.). 412 pp. New York, Churchill Livingstone, 1978. $37.50.

Pain: New Perspectives in Measurement and Management. A. W. Harcus (ed.). 194 pp. New York, Churchill Livingstone. 1977. $23.50.

Cervical Pathology and Colposcopy: Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy. E. Burghart (ed.). 146 pp. Littleton, Thieme-PSG Publishing Company, Inc., 1978.

Emergency Care Handbook: How to Deal With People in Emergencies. Arthur R. Ciancutti. 100 pp. Westport, Technomic Publication. 1977.

Oxygen Transport to Tissue-II. I. A. Silver. 795 pp. New York, Plenum Press, 1977. $49.50.

Bone Tumors: General Aspects and Data on 6,211 Cases. Third Edition. David C. Dahlin (ed.). 445 pp. Springfield: Charles C Thomas Publishers, 1978.

Surgery of the Stomach and Duodenum. Lloyd M. Nyhus and Christopher Wastell (eds.). 788 pp. Boston, Little, Brown and Company, 1977.

Surgery of the Pancreas. Avram M. Cooperman and Stanley O. Hoerr (eds.). 257 pp. St. Louis, C. V. Mosby Company, 1977. $42.50.

Current Contents in Parenteral Nutrition. J. M. Greep, P. B. Soeters, R. I. C. Wesdorp, C. W. R. Phaf, and J. E. Fischer (eds.). 368 pp. The Hague, Martinus Nijhoff—Medical Division. 1977.

Year Book of Cancer—1977. R. E. Clark and R. W. Cumley (eds.). 450 pp. Chicago: Year Book Medical Publishers, 1977. $24.75.

Management of Primary Bone and Soft Tissue Tumors. 21st Annual Clinical Conference on Cancer—M. D. Anderson Hospital. 474 pp. Chicago, Year Book Medical Publishers, 1977. $37.95.

Hamilton Bailey's Emergency Surgery. Tenth edition. H. A. F. Dudley (ed.). 1017 pp. Chicago, Year Book Medical Publishers, 1977. $57.50.

Year Book of Urology—1977. John J. Grayhack (ed.). 392 pp. Chicago, Year Book Medical Publishers, 1977. $21.00.

Disorders of the Lumbar Spine. A. J. Helfet and D. M. Gruebel Lee. 262 pp. Philadelphia, J. B. Lippincott Company, 1977. $22.00.

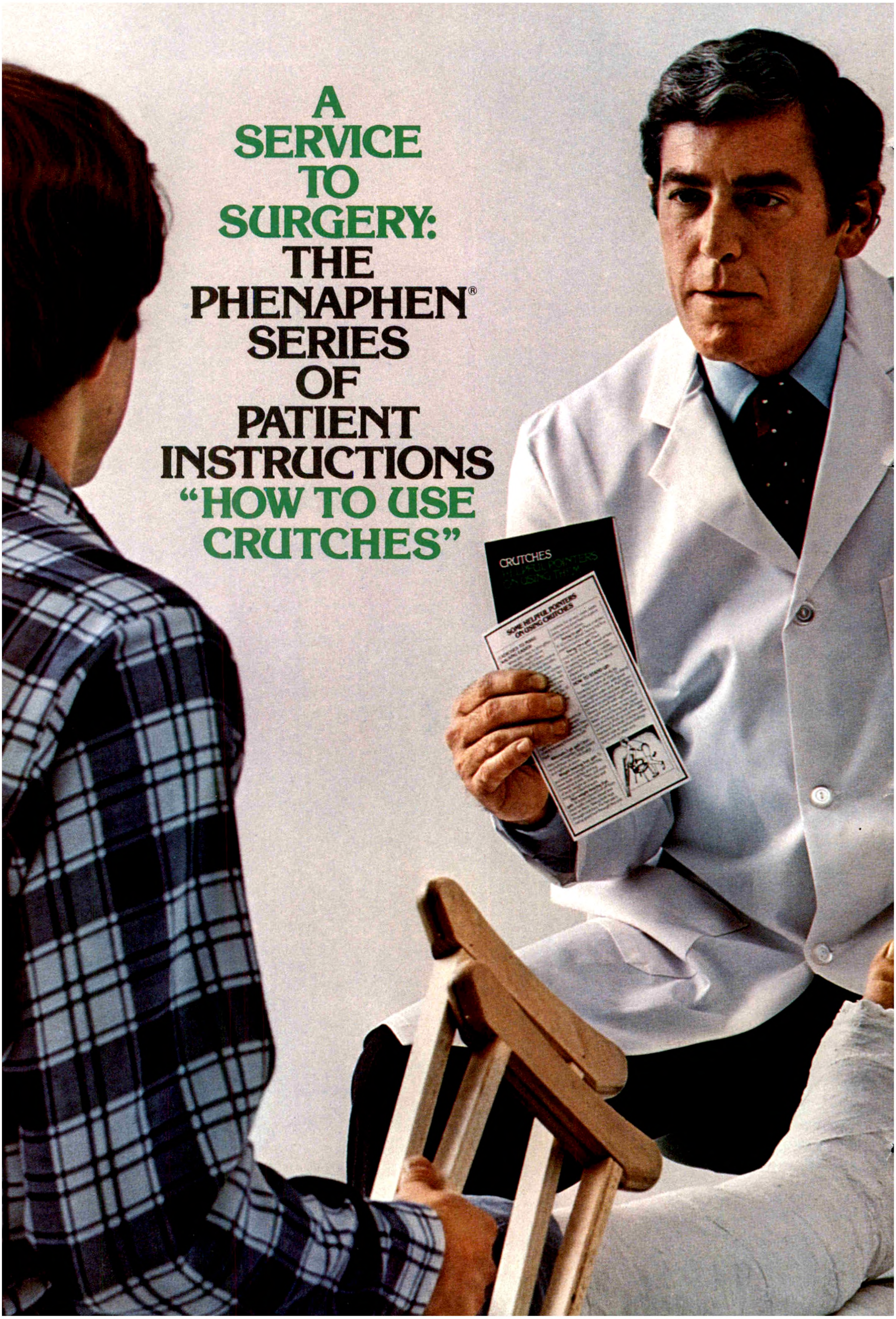
Human Joints and their Artificial Replacements. P. S. Walker. 510 pp. Springfield: Charles C Thomas, 1977.

Current Practice in Orthopaedic Surgery—1977. J. P. Ahstrom (ed.). 271 pp. St. Louis, C. V. Mosby Company, 1977. $29.50.

Secondary Spread in Breast Cancer. B. A. Stoll (ed.). 244 pp. Chicago, Year Book Medical Publishers, 1977.

Facial Injuries. R. C. Schultz. 480 pp. Chicago, Year Book Medical Publishers, 1977. $52.50.

(continued on page 69A)


A SERVICE TO SURGERY:
THE PHENAPHEN® SERIES OF PATIENT INSTRUCTIONS
"HOW TO USE CRUTCHES"
CRUTCHES
HELPFUL POINTERS ON USING THEM
SOME HELPFUL POINTERS ON USING CRUTCHES
HOW TO STAND UP

PRACTICAL ADVICE

At A.H. Robins, we believe that making it easier for the patient to follow your instructions is just as much our obligation as providing you with useful pharmaceutical products.

And making it easier—for both of you—is the whole idea of this, the second in a series of Phenaphen Patient Pads: convenient, preprinted instructions ready for you to tear off and personalize with any minor changes you feel necessary or desirable for the patient who must use crutches.

Informative patient aids can reduce legal risks for the physician as much as 50%.* But even more important, when your instructions are written, they're more likely to be remembered...and followed. And that's what good medicine is all about.

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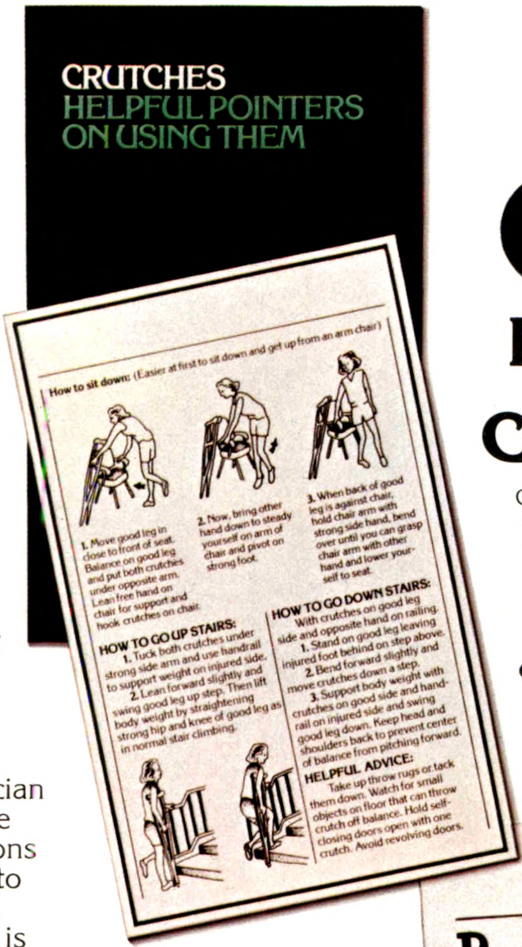
Phenaphen Service to Surgery, A.H. Robins Company,
1407 Sherwood Avenue, Richmond, Va. 23220.

*Patient Care, 7;4, pp. 119-27. Feb. 15, 1973.



CRUTCHES
HELPFUL POINTERS
ON USING THEM

How to sit down: (Easier at first to sit down and get up from an arm chair)

1. Move good leg in close to front of seat. Balance on good leg and put both crutches under opposite arm. Lean free hand on chair for support and hook crutches on chair.

2. Now, bring other hand down to steady yourself on arm of chair and pivot on strong foot.

3. When back of good leg is against chair, hold chair arm with strong side hand, bend over until you can grasp chair arm with other hand and lower yourself to seat.

HOW TO GO UP STAIRS:
1. Tuck both crutches under strong side arm and use handrail to support weight on injured side.
2. Lean forward slightly and swing good leg up step. Then lift body weight by straightening strong hip and knee of good leg as in normal stair climbing.

HOW TO GO DOWN STAIRS:
With crutches on good leg side and opposite hand on railing.
1. Stand on good leg leaving injured foot behind on step above.
2. Bend forward slightly and move crutches down a step.
3. Support body weight with crutches on good side and handrail on injured side and swing good leg down. Keep head and shoulders back to prevent center of balance from pitching forward.

HELPFUL ADVICE:
Take up throw rugs or tack them down. Watch for small objects on floor that can throw crutch off balance. Hold self-closing doors open with one crutch. Avoid revolving doors.

POTENT ANALGESIA

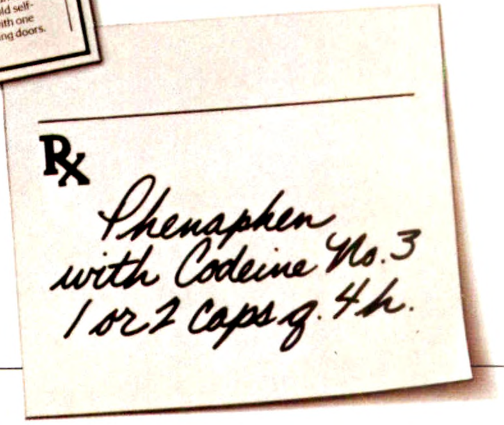
CIII

PHENAPHEN® WITH CODEINE No.3

Codeine Phosphate, USP—30 mg
(Warning: May be habit forming)
Acetaminophen, USP—325 mg

"The black and green capsule with codeine."

- A pharmaceutically elegant capsule
- Easier to swallow than a tablet
- Economical for the patient



℞ Phenaphen
with Codeine No. 3
1 or 2 Caps q. 4 h.

CIII

Phenaphen® with Codeine No. 2
Codeine Phosphate, USP—15 mg
(Warning: May be habit forming)
Acetaminophen, USP—325 mg

CIII

Phenaphen® with Codeine No. 3
Codeine Phosphate, USP—30 mg
(Warning: May be habit forming)
Acetaminophen, USP—325 mg

CIII

Phenaphen® with Codeine No. 4
Codeine Phosphate, USP—60 mg
(Warning: May be habit forming)
Acetaminophen, USP—325 mg

Indications: Phenaphen with Codeine No. 2 and Phenaphen with Codeine No. 3 are indicated for the relief of mild to moderate pain. Phenaphen with Codeine No. 4 is indicated for the relief of moderate to severe pain.
Contraindications: Hypersensitivity to acetaminophen or codeine.
Warnings: *Drug dependence.* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients. Caution patients that acetaminophen and codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants. Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) may exhibit additive CNS depression; when used together reduce dose of one or both.

Usage in Pregnancy. Safe use is not established. Should not be used in pregnant patients unless potential benefits outweigh possible hazards.
Precautions: *Head injury and increased intracranial pressure.* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal condition. Acetaminophen and codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients. Administer with caution to elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.
Adverse Reactions: Most frequent are lightheadedness, dizziness, sedation, nausea, and vomiting; more prominent in ambulatory than in nonambulatory patients; some may be alleviated if patient lies down; other: euphoria, dysphoria, constipation and pruritus.
Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings.

For symptoms and treatment of overdosage and full prescribing information, see product literature.

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ETHICON DOES IT AGAIN

VICRYL* (Polyglactin 910) suture

Improved braided construction results in:

Superior smoothness
Better knot security
Improved handling characteristics
—In addition to the other benefits VICRYL suture is known for. Available dyed and undyed on a wide variety of needles.

Available braided, dyed and undyed.

ETHICON
the closing word

Revised 6/77

VICRYL* (Polyglactin 910) suture

COMPLETE PRODUCT INFORMATION

VICRYL* (Polyglactin 910)
Synthetic Absorbable Suture

DESCRIPTION VICRYL (polyglactin 910) synthetic absorbable suture is prepared from a copolymer of glycolide and lactide. These substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$

VICRYL sutures are sterile, inert, nonantigenic, nonpyrogenic, and elicit only a mild tissue reaction during absorption The braided and monofilament sutures are colored violet to enhance visibility in tissue The braided suture is also available undyed (natural)

ACTIONS Two important characteristics describe the *in vivo* behavior of absorbable sutures: first tensile strength retention, and second, the absorption rate (loss of mass)

Subcutaneous tissue implantation studies of VICRYL suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained

Intramuscular implantation studies in rats show that the absorption of VICRYL suture is minimal until about the 40th post-implantation day Absorption is essentially complete between the 60th and 90th days

INDICATIONS VICRYL synthetic absorbable suture is intended for use as an absorbable suture or ligature

CONTRAINDICATIONS This suture, being absorbable, should not be used where extended approximation of tissues under stress is required

WARNINGS The safety and effectiveness of VICRYL (polyglactin 910) suture in neural tissue, and in cardiovascular surgery have not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize

PRECAUTIONS VICRYL suture knots must be properly placed to be secure. Place the first throw in precise position for the final knot, using a double loop, tie the second throw square, using horizontal tension; additional throws are advisable

Skin and conjunctival sutures remaining in place longer than 7 days may cause localized irritation and should be removed as indicated.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds

ADVERSE REACTIONS Reactions reported in clinical trials which may have been suture related have been minimal. These include skin redness and induration, rare instances of hemorrhage, anastomotic leakage, wound separation in the eye, and abscesses

DOSAGE AND ADMINISTRATION Use as required per operation.

HOW SUPPLIED VICRYL sutures are available sterile, as braided dyed (violet) and undyed (natural) strands in sizes 3 to 8-0, in a variety of lengths, with and without needles, and on LIGAPAK* ligating reels VICRYL sutures, monofilament, dyed (violet) are available in sizes 9-0 and 10-0, in a variety of lengths with needles

Also available in sizes 1 to 4-0 attached to CONTROL RELEASE* needles.

*Trademark

ETHICON

(continued from page 65A)

Dictionary of Medical Ethics. A. S. Duncan, G. R. Dunstan and R. B. Welbourn (eds.). 336 pp. London, Darton Longman & Todd, Ltd., 1977.

The Practice of Coronary Artery Bypass Surgery. D. W. Miller, Jr. 237 pp. New York, Plenum Medical Publishers, 1977.

Year Book of Orthopedics and Traumatic Surgery—1977. M. B. Conventry (ed.). 430 pp. Chicago, Year Book Medical Publishers, 1977. $22.95.

Reconstructive Microsurgery. By R. K. Daniel, and J. K. Daniel. 491 pp. Boston, Little, Brown and Company, 1977. $48.50.

Cleft Craft—The Evolution of its Surgery in Bilateral and Rare Deformities, Vol. II. D. R. Millard. 922 pp. Boston, Little, Brown and Company, 1977.

Fundamentals of Clinical Immunology. J. W. Alexander and R. A. Good. 338 pp. Philadelphia, W. B. Saunders Company, 1977. $11.75.

Biological Aspects of Reconstructive Surgery. D. A. Kernahan and L. M. Vistnes. 417 pp. Boston, Little, Brown and Company, 1977. $28.50.

Progress in Lymphology. R. C. Mayall and M. H. Witte. 389 pp. New York, Plenum Press, 1977. $39.50.

Clinical Biochemical and Hematological Reference Values in Normal Experimental Animals. B. M. Mitruka and H. M. Rawnsley. 272 pp. New York, Masson Publishing USA, Inc., 1977.

Developments in Digestive Diseases. J. E. Berk. 200 pp. Philadelphia: Lea & Febiger, 1977. $22.50.

Atlas of Vaginal Surgery. G. Sani and L. Kos. 201 pp. New York, John Wiley & Sons, 1977.

Proceedings of the XX Biennial World Congress of the International College of Surgeons, Vols. I, II, III. N. C. Louros and D. Le Vay (eds.). Amsterdam, Exerpta Medica, 1977. $163.50/set.

The Source Book of Plastic Surgery. F. McDowell. 509 pp. Baltimore, Williams & Wilkins Company, 1977. $49.95.

Pye's Surgical Handicraft. Twentieth edition. J. Kyle (ed.). 744 pp. Chicago, Year Book Medical Publishers, 1977. $24.75.

Shaw's Textbook of Operative Gynaecology. Fourth edition. Revised by J. Howkins, and C. N. Hudson. London, Churchill Livingstone, 1977. $75.00.

Oxytocin, Vol I. J. S. Roberts. 82 pp. Montreal, Eden Press, 1977 $12.00.

Atlas of Surgery in the First Six Months of Life. S. F. Redo. 188 pp. Hagerstown, Harper & Row, Publishers, Inc., 1978. $27.50.

Psychosocial Care of the Dying Patient. C. A. Garfield (ed.). 430 pp. New York, McGraw-Hill Book Company, 1978.

Posture. R. Roaf. 100 pp. New York, Academic Press, 1977. $7.50.

Fracture Management: A Practical Approach. J. T. Hartman. 388 pp. Philadelphia, Lea & Febiger, 1978.

Gynecologic Operations. H. M. M. Tovell and L. D. Dank. 321 pp. Hagerstown, Harper & Row, Publishers, Inc., 1978. $30.00.

Pheochromocytoma. W. M. Manger and R. W. Gifford, Jr. 398 pp. New York, Springer-Verlag, 1977. $49.80.

Renin. S. Oparil and R. Katholi. 322 pp. Montreal, Eden Press, Inc., 1978. $24.00.

Lithium and Animal Behavior. D. F. Smith. 66 pp. Montreal, Eden Press, Inc., 1978. $12.00.

Proteins of Animal Cell Plasma Membranes. By D. F. H. Wallach. 154 pp. Montreal, Eden Press, Inc., 1978. $16.00.

Reliable and safe hemostat

to help control small-vessel bleeding without injuring vital tissue

SURGICEL

TRADEMARK

Absorbable Hemostat

(oxidized regenerated cellulose)

SURGICEL Absorbable Hemostat
TRADEMARK
(oxidized regenerated cellulose)

FOR SURGICAL USE

(For dental applications of this product, reference should be made to the package insert for dental use.)

DESCRIPTION: SURGICEL Absorbable Hemostat is a chemically-sterilized, absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and can be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance.

ACTIONS: The mechanism of action whereby SURGICEL accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors including the amount used, degree of saturation with blood, and the tissue bed.

INDICATIONS: SURGICEL Absorbable Hemostat (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective.

CONTRAINDICATIONS: Although packing or wadding sometimes is medically necessary, SURGICEL Absorbable Hemostat should not be used in this manner unless it is to be removed after hemostasis is achieved.

SURGICEL should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

When SURGICEL is used to help achieve hemostasis around the spinal cord in laminectomies, or around the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure.

SURGICEL should not be used to control hemorrhage from large arteries.

SURGICEL should not be used on *non-hemorrhagic serous oozing surfaces,* since body fluids other than whole blood, such as serum, do not react with SURGICEL to produce satisfactory hemostatic effect.

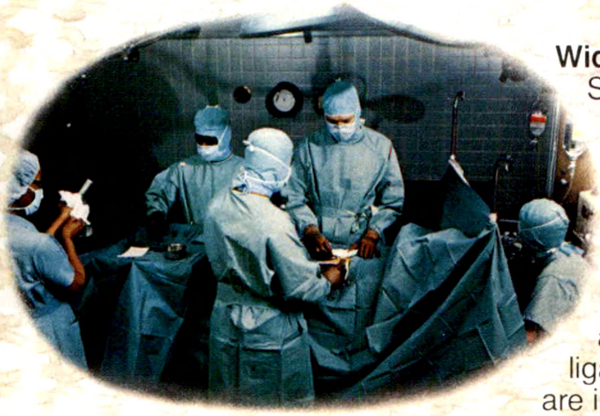
WARNINGS: SURGICEL Absorbable Hemostat is supplied sterile and should not be autoclaved because autoclaving causes physical breakdown of the product.

SURGICEL is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

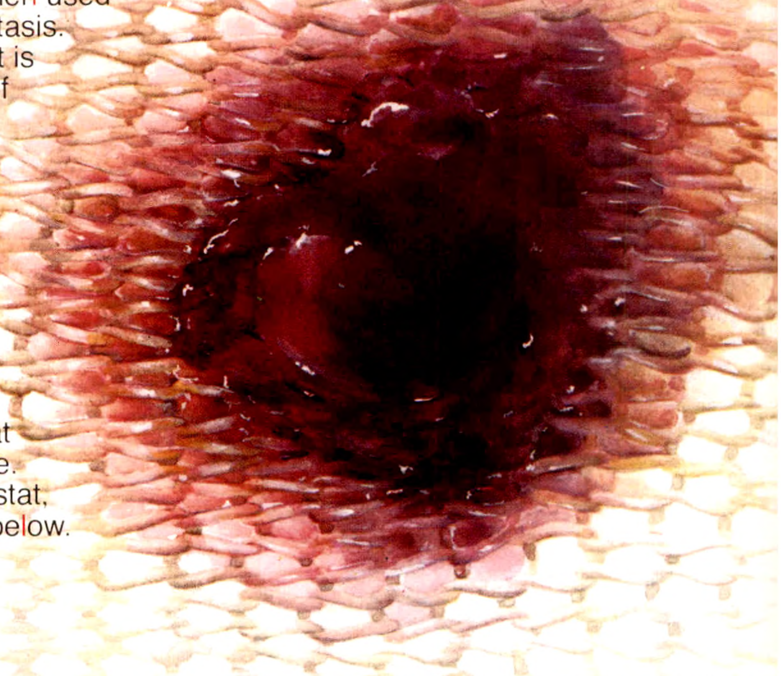
Closing SURGICEL in a contaminated wound without drainage may lead to complications and should be avoided.

The hemostatic effect of SURGICEL is

©Johnson & Johnson 1975



Wide hemostatic application in surgery. SURGICEL* Absorbable Hemostat is a pliable knitted fabric that has been found to be inherently and dependably hemostatic when used as an aid in the control of small-vessel bleeding in abdominal, thoracic, neurosurgical, orthopedic, cardiovascular, gynecologic and otorhinolaryngologic procedures, in superficial open wounds and on donor sites. SURGICEL Absorbable Hemostat is a valuable adjunct in the control of small-vessel bleeding when ligation or other conventional methods of control are impractical or ineffective.



Rapid and complete absorption with virtually no tissue reaction when used properly in minimal amounts for hemostasis. SURGICEL Absorbable Hemostat is completely absorbable from sites of implantation after it has become a gelatinous mass that aids in the formation of a clot.

Convenient to use. SURGICEL Absorbable Hemostat requires no additional hemostatic preparation; it is ready for use directly from the vial. When exposed to blood, it adheres readily to tissues but generally not to dry instruments or dry surgical gloves. SURGICEL Absorbable Hemostat should be stored at controlled room temperature. Before using SURGICEL Absorbable Hemostat, please refer to product information below.

greater when it is applied dry; therefore it should not be moistened with water or saline.

SURGICEL should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved. It *must* always be removed from the site of application after use in laminectomy procedures and from foramina in bone when hemostasis is obtained. This is because SURGICEL, by swelling, may cause nerve damage by pressure in a bony confine. Paralysis has been reported when used around the spinal cord, particularly in surgery for herniated intervertebral disc.

PRECAUTIONS: Use only as much SURGICEL Absorbable Hemostat as is necessary for hemostasis, holding it in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction.

SURGICEL should be applied loosely against the bleeding surface. Wadding or packing should be avoided, especially within rigid cavities, where swelling may interfere with normal function or possibly cause necrosis.

In *urological procedures,* minimal amounts of SURGICEL should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.

Since absorption of SURGICEL could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.

If SURGICEL is used temporarily to line the cavity of large open wounds, it should be placed so as not to overlap the skin edges. It should also be removed from open wounds by forceps or by irrigation with sterile water or saline solution after bleeding has stopped.

Precautions should be taken in *otorhinolaryngologic surgery* to assure that none of the material is aspirated by the patient. (Examples: controlling hemorrhage after tonsillectomy and controlling epistaxis.)

Care should be taken not to apply SURGICEL too tightly when it is used as a wrap during vascular surgery (see "ADVERSE REACTIONS" section).

ADVERSE REACTIONS: "Encapsulation" of fluid and foreign body reactions have been reported.

There have been two reports of stenotic effect when SURGICEL Absorbable Hemostat has been applied as a wrap during *vascular surgery*. Although it has not been established that the stenosis was directly related to the use of SURGICEL, it is important to be cautious and avoid applying the material tightly as a wrapping.

Possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy have been reported. There has been one report of a blocked ureter after kidney resection, in which postoperative catheterization was required.

Occasional reports of "burning" and "stinging" sensations and sneezing when SURGICEL has been used as packing in epistaxis, are believed due to the low pH of the product.

Burning has been reported when SURGICEL was applied after nasal polyp removal and after hemorrhoidectomy. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL was applied on surface wounds (varicose ulcerations, dermabrasions, and donor sites) also have been reported.

SURGIKOS
A Johnson & Johnson Company
New Brunswick, New Jersey 08903

*Trademark of Johnson & Johnson

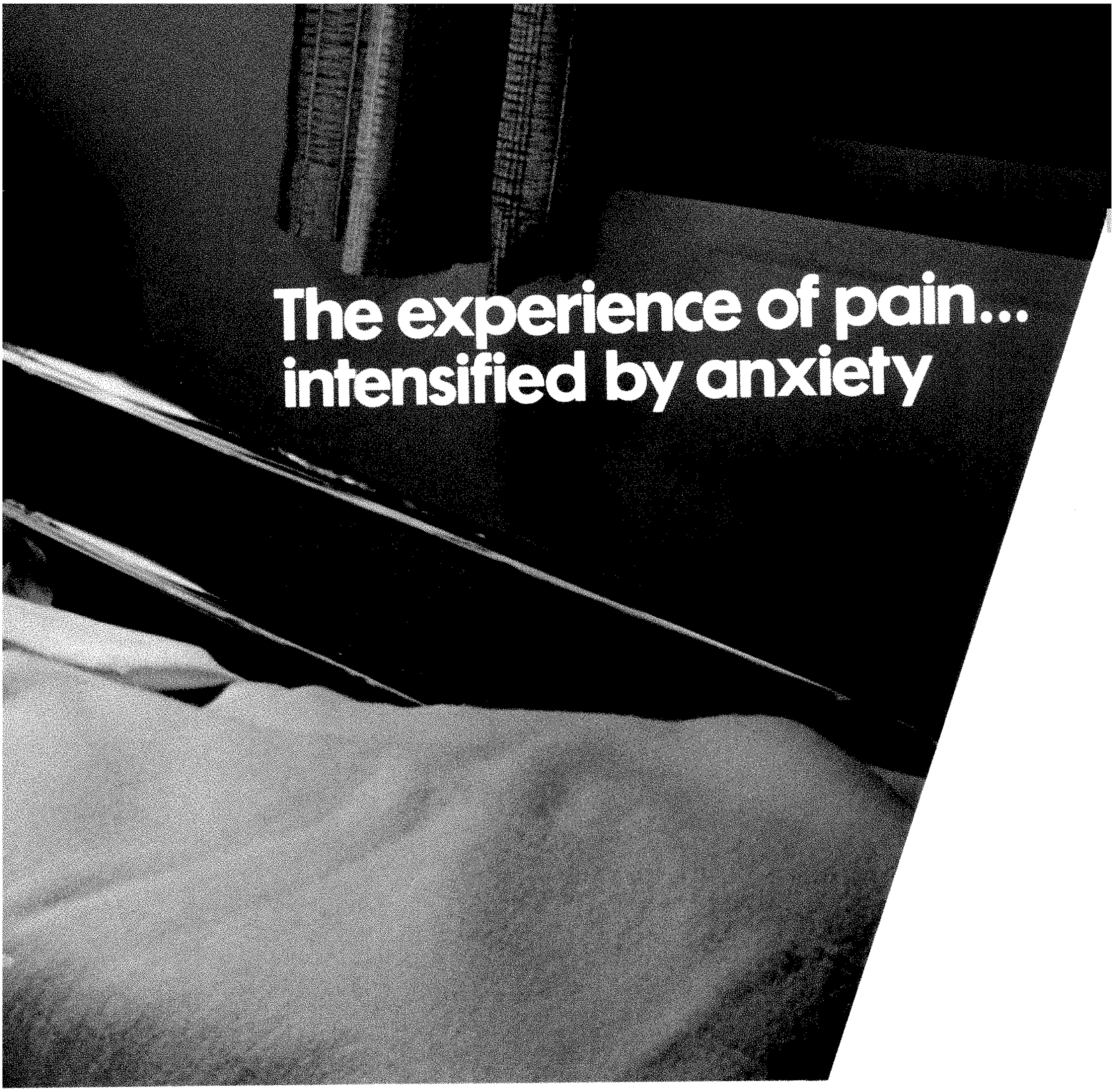
Injectable Valium®(diazepam) reduces anxiety associated with pain

In the postoperative patient, pain is a major stress that can compound other psychological stresses of hospitalization, e.g., separation anxiety, fear of injury to the body's integrity. The excess anxiety generated by the patient's perception of or emotional response to pain may itself intensify the pain.[1, 2] Used adjunctively with analgesics, Injectable Valium provides a prompt calming action for the anxiety associated with the pain.

Narcotic analgesic dosage can and should be reduced

When Injectable Valium is used with narcotic analgesics, dosage of the narcotic should be reduced by at least one-third. In some cases use of a narcotic may not be necessary.

1. Wallace PGM, Norris W: *Br J Anaesth 47:* 113-120, 1975
2. Strain JJ: The problem of pain, in *Psychological Care of the Medically Ill: A Primer in Liaison Psychiatry,* edited by Strain JJ, Grossman S. New York, Appleton-Century-Crofts, 1975, pp. 93-107



Injectable
Valium®
(diazepam) ⓘⓥ

adjunctively for excess anxiety associated with pain

Please see following page for a summary of product information.

ROCHE

Injectable Valium® (diazepam) Ⓒ IV

Ready-to-use 2-ml Tel-E-Ject® (disposable syringes), 2-ml ampuls, 10-ml vials } 5 mg/ml

☐ promptly controls anxiety/tension before and after surgery

☐ reduces anxiety associated with pain

☐ narcotic analgesic dosage can and should be reduced

☐ use with care in elderly, very ill and those with limited pulmonary reserve (See Warnings section below)

can help the surgical patient every step of the way

Please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms (similar to those with barbiturates, alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal/muscle cramps, vomiting, sweating). Keep addiction-prone individuals under careful surveillance because of predisposition to habituation/dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics,or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium (diazepam) directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Book Reviews

The Treatment of Venous Disorders. John T. Hobbs (ed.) 438 pp. Philadelphia, J. B. Lippincott Company. 1977.

THE SUBTITLE OF THIS BOOK describes it as providing "a comprehensive review of current practice in the management of varicose veins and the postthrombotic syndrome." In the event, the book does both more and less than this: more, because the subject matter is broader than the title implies; and less, because the review is comprehensive in only rather a special sense.

There are brief but useful accounts of the anatomy, epidemiology and heredity of varicose veins, and of various methods for investigating the venous system. Within outstandingly comprehensive reviews of the prevention and management of deep vein thrombosis by Nicolaides and his colleagues are also considered the attack-rate and natural history of this condition.

The special sense in which the review of treatment is comprehensive resides in its internationalism: by way of contributions from Great Britain, Eire, the U.S.A., Argentina, Norway, Sweden, Denmark, West Germany, Switzerland, Russia and South Africa one is taken on a world tour to discover how experts treat the various disorders of veins. The analogy is a close one, for as is often the case on such grand tours, the opinions given are very personal, very authoritative—but sometimes lacking in the sorts of objectively-gathered data that carry conviction. An outstanding exception to this caveat is the comparative study by Hobbs of surgical and sclerosant treatment for varicose veins. A special bonus gained from the European leg of the tour are the descriptions of methods for the cosmetic treatment of dilated intracutaneous veins, a subject to which little attention is given in many texts.

For any surgeon who has to do with disorders of veins this is a good book to read: for detailed information in some fields, for new ideas in others.

JOHN LUDBROOK, M.D.

Brief Textbook of Surgery. Artz, Cohn and Davis. 694 pp. Philadelphia, W. B. Saunders Co. 1976.

THIS IS AN UNUSUALLY GOOD "synopsis of surgery" by virtue of its being designed to cover the surgical topics with which all undergraduate medical students should be familiar. The text is an outgrowth of a study by the Board of Governors of the American College of Surgeons of "core" surgical knowledge. The distinguished group of authors, many of them members of the study group, have presented their subjects in a clear and easily read manner. The book is compact and makes use of pertinent and succinct illustrations and tables.

Some surgical educators might argue that there should be more detail in one or another subject area or additional chapters on Surgical History or Ethics. However, the editors have done an admirable job of paring the fat from the discussions, leaving the meat for the student who has only a few weeks to cover the broad subject of surgery. It has been correctly pointed out in the Preface that the student who intends to pursue postgraduate training in surgery must master the larger standard textbooks in surgery. However, for the majority of medical students doing a required clerkship in the operative specialties, this is a book to be recommended as broad, informative, authoritative and interesting to read.

RONALD K. TOMPKINS, M.D.

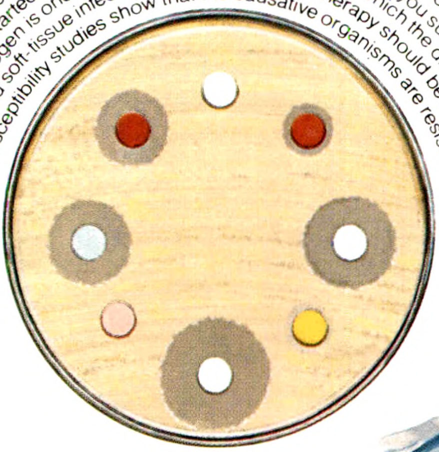
Symposium on "Fat Emulsions in Parenteral Nutrition. H. C. Meng and D. W. Wilmore (eds.) 124 pp. Chicago, American Medical Association. 1976.

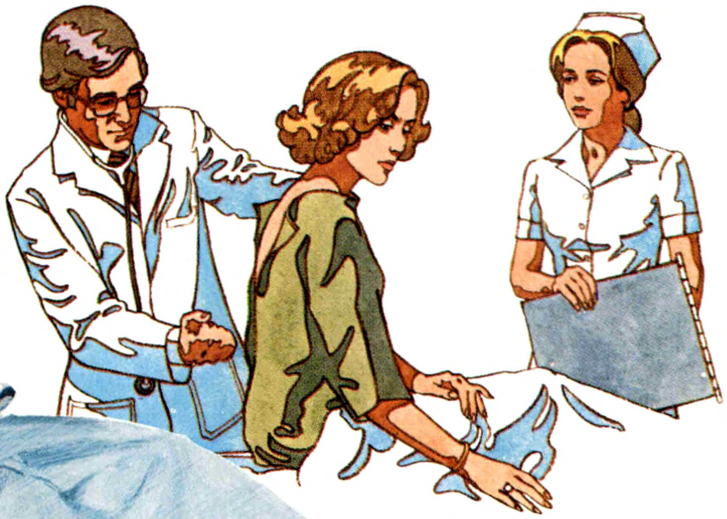
THIS BOOK IS THE PUBLISHED VERSION of a recent symposium on fat emulsions for intravenous use sponsored by the AMA Nutrition Advisory Group. The subject is important since there is a need for a safe, effective fat emulsion and of current interest since something like this may be on the horizon. A strong point is that essentially all of the major groups engaged in lipid research and experienced in the use of fat emulsions are represented. However, like many edited volumes, there is excessive overlap between some chapters. The editors have achieved reasonable organization of the material and the book is easily read, attractively printed, and well-illustrated.

The book is divided into three parts dealing with the majority of the currently available knowledge of the subject. The first has to do with the metabolism and function of essential fatty acids, essential fatty acid deficiency in patients on total parenteral nutrition, and details related to the correction of deficiency with intravenous fat. An excellent description of the relationship between unsaturated fatty acids and prostaglandins is given as well as the related biological considerations. The second section deals

(continued on page 81A)

Appropriate cultures should be taken, but Keflin® (cephalothin sodium, Lilly) may be started before susceptibility results are obtained if you suspect the causative pathogen is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections.* Other antibiotic therapy should be instituted if susceptibility studies show that the causative organisms are resistant.

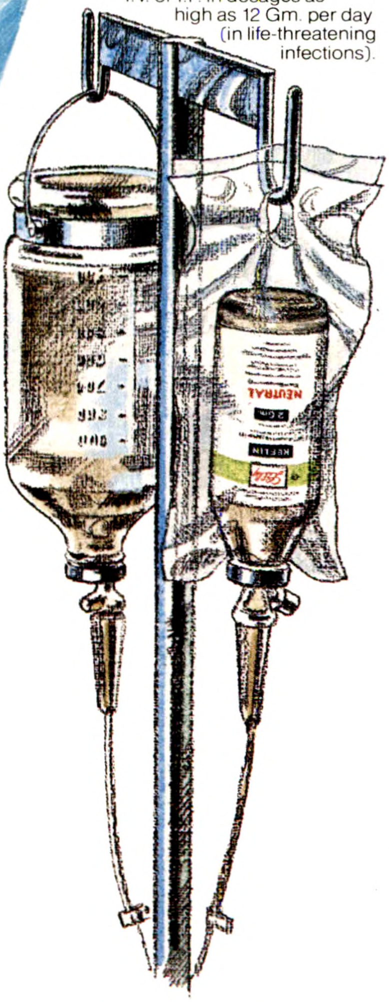


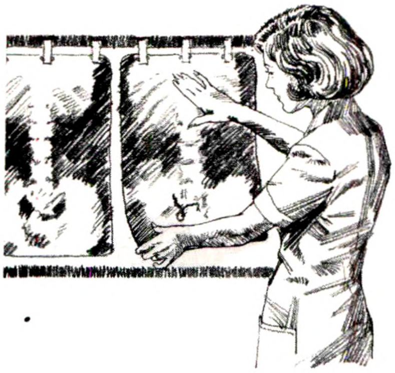


In the immunosuppressed patient, usual clinical signs and symptoms of infection may be missing or not clear. Hence, diagnosis and initiation of proper therapy become most urgent.

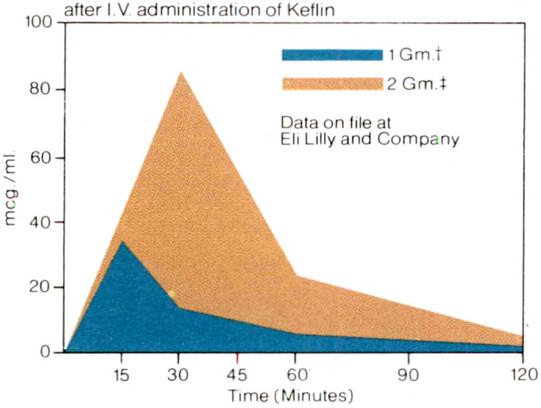
An initial loading dose of 1 to 2 Gm. of Keflin may be given regardless of the patient's renal status. Patients with impaired renal function should be placed on a reduced dosage schedule. Usual doses in such individuals may result in excessive serum concentrations.

Keflin may be administered I.V. or I.P. in dosages as high as 12 Gm. per day (in life-threatening infections).





Mean serum concentrations after I.V. administration of Keflin



†Administered to six patients by rapid I.V. infusion.

‡Administered to ten patients over a thirty-minute period.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

Please see opposite page for summary of prescribing information.

In serious skin and soft-tissue infections*

OFTEN USEFUL WHEN MOST NEEDED

As you know, skin and soft-tissue infections* including peritonitis, may progress with alarming rapidity in patients with impaired host defenses... even to the point of becoming irreversible. Keflin can often be useful before the infection becomes irreversible... exactly when it is most needed.

Eleven years after its introduction, Keflin continues to be effective against most strains of gram-positive and gram-negative organisms commonly implicated in serious skin and soft-tissue infections.* Therefore, when you suspect that the pathogen involved is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections,* you may begin therapy with Keflin even while results of susceptibility studies are pending... and thus save precious hours for the patient. Keflin may be administered to infants and to patients with reduced renal function.

Keflin should be given cautiously to penicillin-sensitive patients.

It is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Keflin® 2 Gm.† in 100-ml. ampoule

cephalothin sodium

Neutral

for Injection

†Equivalent to cephalothin

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin® (cephalothin sodium, Lilly), Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy – Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

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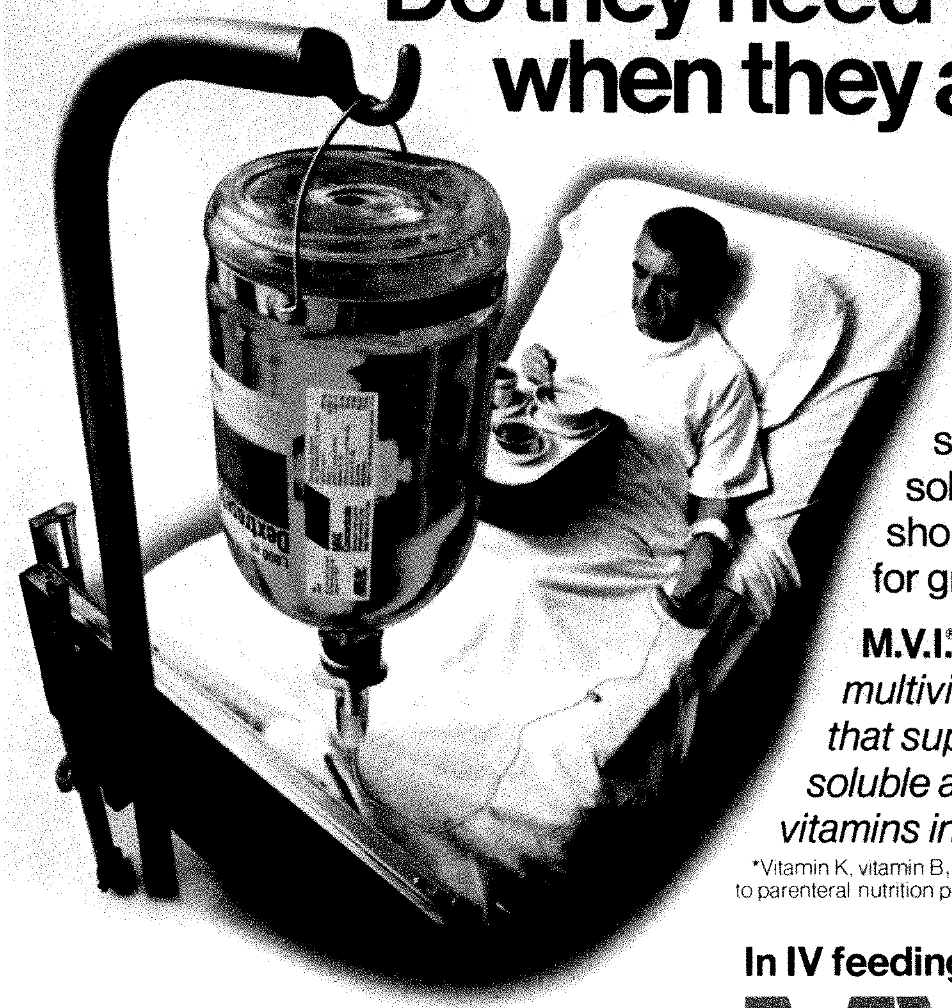

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A Clinicopathologic Study of 21 Cases of Pancreatic Cystadenocarcinoma

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Cystadenocarcinomas are rare tumors of the pancreas. They are half as common as their benign counterpart—the cystadenoma. A review of 21 cases, including eight reported since 1963, revealed that most patients presented with upper abdominal pain and a large palpable upper abdominal mass. All patients had evidence of malignant degeneration occurring in a mucous cystadenoma. None had evidence of a serous cystadenoma. Grading revealed a predominance of low-grade tumors: 20 of the 21 lesions were grade 1 or 2. Cystadenocarcinomas were slightly more frequent in the head of the pancreas. Four patients had metastasis. Complete excision by distal or total pancreatectomy or Whipple pancreaticoduodenectomy is recommended. The five year survival after complete excision is 68%, and for patients with grade 1 lesions, and five year survival is 64%.

CYSTADENOCARCINOMA IS A RARE malignant tumor of the pancreas, accounting for about 1% of all pancreatic malignancies. The lesion is seen about half as frequently as its benign counterpart, the cystadenoma, according to Becker and associates.[1]

The first case reported in the American literature was by Lichtenstein in 1934.[9] He described a 44-year-old woman who at autopsy had a large papillary cystadenocarcinoma of the pancreatic tail with metastatic liver nodules and peritoneal seeds. Many isolated reports and several reviews appeared during the subsequent three decades after this initial report. Kennard in 1941[7] reviewed the world literature and added one case of papillary cystadenocarcinoma. At that time, most tumors either were biopsied only or were treated with internal or external drainage procedures or marsupialization. Sawyer and associates in 1952[12] found reports of only 29 cases of cystadenocarcinoma and added another to the literature. Most reports concerned clarifying the incidence of the tumors and assessing the malignant potential. Information on the natural history, pathogenesis, and prognosis was not forthcoming because no one institution had a large enough series with pathologic confirmation, surgical treatment, and long-term follow-up.

In 1963, Cullen, ReMine, and Dahlin[4] reported 17 acceptable cases from 42 cases of cystadenocarcinoma at the Mayo Clinic. They noted that seven of 11 patients treated by complete surgical excision survived. This experience was similar to that reported by Warren and Hardy in 1968,[13] who found that seven of 17 patients treated with resection had good results. The most recent case reports by Bilton et al.,[2] Johnson,[6] Rask,[10] and Ribet et al.[11] noted the slow-growing nature of these tumors and success after total resection of the cystadenocarcinoma.

Material

Between 1928 and 1974, there were more than 50 cases of cystadenocarcinoma of the pancreas on record in the tissue registry clinical files and autopsy files at the Mayo Clinic. The present study involves the review of 21 patients with cystadenocarcinoma. All cases accepted for review satisfied the following criteria: 1) adequate pathologic material available for review, classification, and grading; 2) primary surgical treatment at our institution; 3) follow-up of all patients and their status in 1976 or to death with cause of death being available from autopsy reports; and 4) clinical records evaluated to ascertain pertinent clinical features. Excluded from this study were cases in which 1) tissue was inadequate for classification and grading; 2) autopsy specimens were not available; 3) initial surgery was not done at our institution; 4) follow-up data or autopsy reports were not available; and 5) lesions found at autopsy were not suspected during life.

The present review adds eight new cases since the last review in 1963.[4] Four of the cases reviewed in 1963 did not satisfy the above criteria.

Reprint requests: Dr. D. J. Hodgkinson, c/o Section of Publications, Mayo Clinic, 200 First Street SW, Rochester, MN 55901.

Submitted for publication: November 26, 1977.

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TABLE 1. *Symptoms of 21 Patients With Cystadenocarcinoma of the Pancreas*

Symptom	No. of Patients
Abdominal pain	17
Loss of weight	9
Jaundice	6
Belching excessive gas	6
Nausea and vomiting	5
Bleeding	3
Diarrhea	2
Weakness and fatigue	1
Dyspnea	1
Asymptomatic	0

Clinical Findings

Age and Sex

The age range of the 21 patients (11 women and ten men) was 40–73 years, with a mean of 61.3 years: two patients were in the fifth decade, six in the sixth, ten in the seventh, and three in the eighth. The sex ratio was somewhat different from that in the previous report,[4] in which there were 13 women and four men. In patients with the benign counterpart of the cystadenocarcinoma—the cystadenoma—the average age was 55 years and the females predominated 4.6 to one. Malignant cystadenocarcinoma has not been found in any child who was in the first decade as stated by Grosfeld et al.[5] In contradistinction to Becker and coworkers' report[1] that cystadenocarcinoma occurs at a younger age than does the solid pancreatic cancer, our patients were about the same age as those with conventional solid pancreatic malignancy.

Symptoms

The most frequent symptom was pain. Seventeen patients (81%) had pain as all or part of their symptom complex at presentation (Table 1). Three patients had pain as their only complaint, and another three had pain accompanied by loss of weight and belching. Often, the pain lasted for years, but its characteristics were vague, frequently being described as an epigastric distress after meals or as mild discomfort and a feeling of upper abdominal fullness or "pressure." One patient had an eight year history of vague upper abdominal pain, and two others had symptoms for six years. In one of these patients, the distress was relieved by bending over; presumably, this allowed the stomach to move away from the upper gastrointestinal tract and relieve the compression. The localization of the pain also was often vague. One patient had periumbilical discomfort; however, in others, the pain was more constantly in the left upper quadrant.

Three patients noted that they had a palpable upper abdominal mass, one for four months and another for ten months before seeking medical attention.

Three patients, one with gross melena, had a recent history of hematemesis. At laparotomy, one patient had a profuse collateral blood supply around the cyst; another had splenic vein occlusion; and a third had hepatic metastasis.

Six patients had jaundice. At laparotomy, one had the common bile duct directly invaded by the pancreatic malignancy. Two patients with jaundice had liver metastasis, and another two had peripancreatic nodal metastasis compressing the extrahepatic biliary ducts. One patient had a large unresectable cystadenocarcinoma of the pancreatic head compressing the common bile duct. Three patients had diabetes mellitus, and no patient had a history of alcoholism or pancreatitis.

Signs

The most frequent clinical sign was a palpable abdominal mass. Twelve patients (57.2%) had a palpable mass: seven in the left upper quadrant, four in the right upper quadrant, and one in the epigastrium and right upper quadrant. In some, the mass was mobile with respiration, and masses in the left upper quadrant were commonly mistaken for enlarged spleens, as Lichtenstein did in his original report in 1934.[9] In six patients (28.5%), the cystadenocarcinoma was an incidental finding during laparotomy, while in three patients, the lesion was suspected but no mass could be palpated abdominally. The characteristics of the mass varied, but most were nontender and firm with dimensions that were large or diffuse.

Diagnostic Investigations

Fifteen patients underwent upper gastrointestinal barium study. Results were "positive" in eight (53%) ("positive" refers to the presence of an extrinsic mass deforming the barium-filled stomach and duodenum). There were no characteristic roentgenographic features of cystadenocarcinoma, and the findings were similar to those of any large retroperitoneal cystic mass. A large smooth displacement of the greater curvature of the stomach to the midline with tail lesions and a similar displacement of the stomach anteriorly with body or head lesions suggest the possibility of a benign or malignant pancreatic cyst. The high success rate of upper gastrointestinal barium studies has been noted by Warren and Hardy,[13] who found ten of 11 patients studied by upper gastrointestinal series had evidence of pancreatic enlargement. Oral or intravenous cholangiography was performed in seven cases but was not helpful in establishing the diagnosis.

Angiography, splenoportography, and radioactive and ultrasonic scanning were not used, but according to Ribet et al.[11] angiography has been reported to be useful in preoperative planning by outlining the mesenteric vessels. Ultrasonic scanning techniques probably will be helpful in identifying the cystic nature of these tumors. The differentiation of primary cystadenoma and cystadenocarcinoma from solid pancreatic malignancy with secondary obstruction of the pancreatic duct or central necrosis still needs to be made by the surgeon and pathologist.

Associated Conditions

Seven patients had associated biliary tract disease. Five had undergone cholecystectomy for cholelithiasis, and two had cholelithiasis at laparotomy. Two patients had a duodenal ulcer, and one complained of periumbilical pain that was different from the usual ulcer pain. One patient had a gastric ulcer secondary to a pyloric ulcer. The presence of ulcers seems not to be related etiologically to the cystadenocarcinoma, although gastrin levels were not available for these patients. Except for one woman with a benign ovarian cyst, no patient had associated cystic disease of any intra-abdominal organ.

Pathologic Features of Lesion

Cystadenocarcinomas occur half as frequently as do their benign counterpart, the cystadenoma. No pancreatic cystadenocarcinoma studied had morphologic characteristics resembling the serous cystadenoma. (Cystadenomas are of two types: serous and mucinous. The mucinous cystadenoma arises from ductal epithelium while the serous type probably arises from the acinar cell. All cystadenocarcinomas have gross and histologic characteristics resembling the mucinous cystadenoma.) Pancreatic cystadenocarcinomas probably arise by malignant degeneration occurring in the benign mucinous cystadenoma. There is no associated inflammatory reaction, as is true of the pancreatic pseudocyst.

Macroscopic Findings

Pancreatic cystadenocarcinomas are rounded, lobulated, or smooth and are usually well-encapsulated lesions arising from normal pancreatic tissue. The surface may be broken by invasive tumor, as it was in eight of our cases. Most often, however, the outside appearance of the tumor gives little indication of its true malignant character.

Cystadenocarcinomas may appear anywhere in the pancreas. Unlike cystadenomas, which are more frequent in the tail of the pancreas, cystadenocarcinomas occur more frequently in the head. In our series, there were eight lesions in the head, five in the tail, four in the body and tail, one in the body, one in the body and head, and one involving the body, head, and tail. In one case, the site was unknown. There were no multiple or pedunculated cystadenocarcinomas.

[redacted]

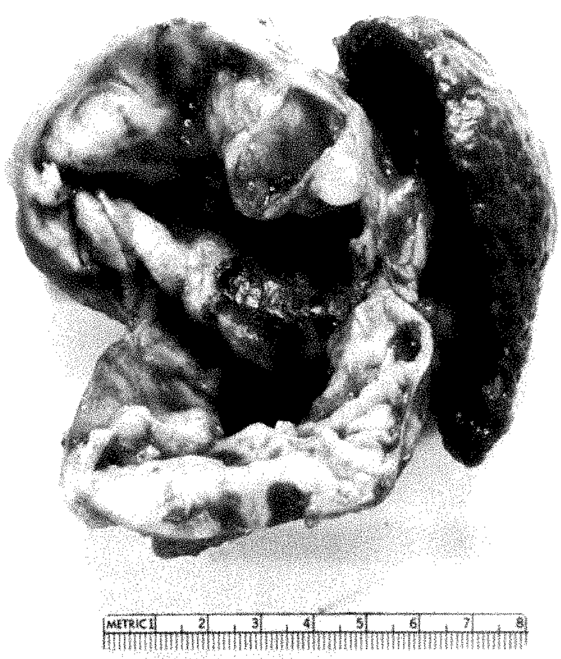

FIG. 1. Macroscopic appearance of cystadenocarcinoma of the pancreatic tail.

The size of the tumors ranged from four to 24 cm in largest diameter, with a mean of 10.1. The mean size of tumors in the head was smaller (4.9 cm) than that in the tail (12.4 cm) or body (13.6 cm).

The sectioned cystadenocarcinoma usually consisted of a large unilocular cyst into which numerous "cauliflower-like" excrescences projected (Fig. 1). Some of the larger cysts had several major subcompartments, but "honeycombing" was not seen as it is in the benign serous cystadenocarcinoma.

The fluid content was often turbid, thick, and gelatinous, and in no instances was it hemorrhagic. The surrounding pancreatic tissue usually was normal; however, six (28%) of the lesions had histologic features of old pancreatitis.

Histopathologic Features

The following microscopic features were noted:

1) The wall of the cyst varied in thickness from 2–15 mm and was composed of a fibrous connective

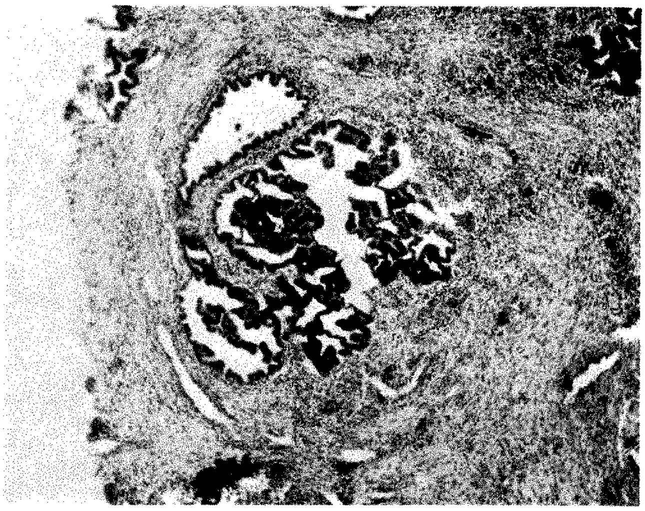

FIG. 2a. Cystadenocarcinoma of the pancreas. Areas of benign epithelial lining and malignant transition (H&E ×64).

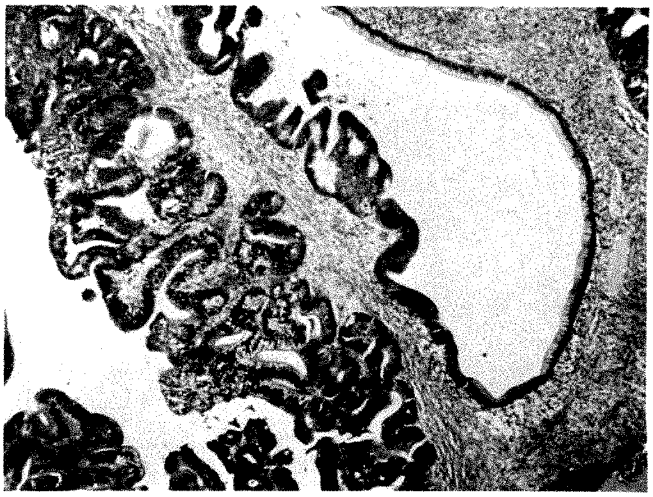

FIG. 2c. Grade 2 cystadenocarcinoma of the pancreas (H&E ×64).

tissue with variable infiltration of leukocytes and lymphocytes.

2) The mucous epithelial lining was folded upon itself and formed projections into the interior of the cyst.
3) All lesions had benign areas—areas characteristic of a mucinous cystadenoma. In none did the benign areas resemble a serous cystadenoma.
4) The epithelial lining cells were columnar and, within the same cyst, were interspersed with areas of frank malignancy. These areas were dedifferentiated, with epithelial "piling," loss of basal nuclear placement, and increasing pleomorphism (Fig. 2A).
5) The grading of malignancy according to Broders' classification[3] revealed predominantly well-differentiated tumors. Eleven lesions were grade 1 (Fig. 2B), nine grade 2 (Fig. 2C), and one grade 3.
6) The stroma was uniformly fibrous, with little chronic inflammatory cell infiltrate. Marked cellularity may be observed in the fibrous stroma.

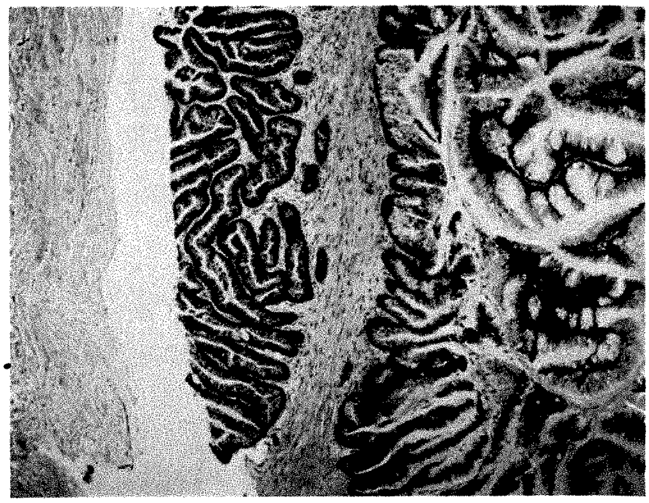

FIG. 2b. Cystadenocarcinoma of the pancreas. Grade 1 (H&E ×64).

Histopathologic Differentiation

The finding of a mucinous cystadenoma should alert the histopathologist to search for malignancy. Multiple samples may be required to be certain of a benign diagnosis. Needle biopsy is inadequate because the chance of obtaining only a benign portion of the tumor is highly likely. The risk of tumor cell spillage also makes biopsy less desirable. Multiple sections may be required to detect an area of malignant change, and these should be detected by the gross examination. Occasionally, the surface of the tumor is involved, and the tumor is attached to adjacent structures. Such attachment should not preclude complete excision. Local tissue and lymph nodes, if suspected of being involved, should be sampled.

Treatment and Follow-Up

Operative Considerations

The site, size, and mobility of the lesion and its relationship to vital structures, its attachment to surrounding structures, and the presence of metastasis influence the type of surgical treatment.

Four (19%) of our patients had metastasis at initial surgery: two with secondary hepatic lesions and two with metastasis confined to peripancreatic nodes. If there is local nodal metastasis, curative resective surgery is still possible. Liver metastasis precludes curative resection. However, palliative bypass surgery can be offered.

TABLE 2. *Surgical Treatment of 21 Patients With Pancreatic Cystadenocarcinoma*

Treatment	No. of Patients
Total excision with tail of pancreas and spleen	7
Whipple	4
Total pancreatectomy	3
Partial excision	3
Bypass	1
Biopsy	3
Total	21

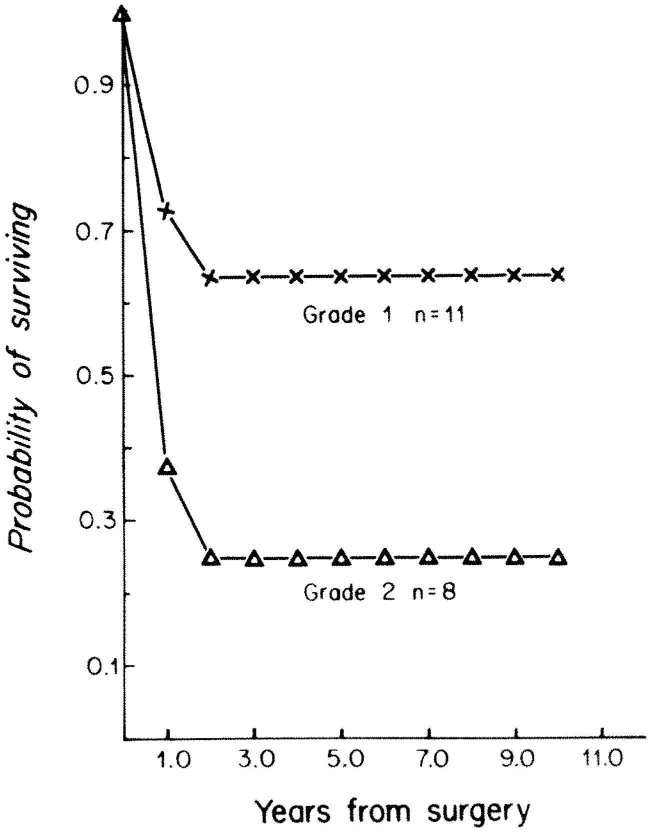

FIG. 3. Patient survival. Grade 1 cystadenocarcinoma compared with grade 2 cystadenocarcinoma.

Only rarely was the blood supply to these tumors profuse. One patient had huge, dilated veins in the retroperitoneum and had presented with upper gastrointestinal hemorrhage (requiring 18 units), presumably secondary to variceal formation by obstruction of the splenic vein from a large cystadenocarcinoma in the pancreatic tail.

For tumors in the tail or body, distal pancreatectomy, including excision of the spleen, can be performed, with hope of cure for these low-grade malignancies.

If the portal vein can be dissected free, lesions in the head of the pancreas can be treated by a Whipple type of pancreaticoduodenectomy or total pancreatectomy. Invasion and ulcers of the duodenum, as reported by Lefaucher,[8] can be surgically removed by pancreaticoduodenectomy, and the prognosis is better than that with noncystic pancreatic malignancies of the head.

The only contraindications for resective management concern the intimate relationship that these tumors may have with the mesenteric vessels or portal vein or the presence of hepatic metastasis or extensive local invasion. Smaller tumors that are suspected of not being malignant can be removed from the pancreas by partial pancreatectomy without a major pancreatic resection.

Surgical Management

Cystadenocarcinomas should be totally excised. There is no indication for internal or external damage of these cystic lesions, as there is for pancreatic pseudocysts. Unlike pseudocysts, unless there is metastasis or extensive invasion of the cyst wall by malignant infiltration, these cysts usually can be separated from the surrounding tissues. All efforts during resective procedures should be directed to removing the cyst intact, because rupture may disseminate malignant cells intraperitoneally. The various modes of treatment are shown in Table 2.

Seven patients had a curative surgical procedure—total excision along with the tail of the pancreas and spleen. Of the 14 other patients, four had Whipple

TABLE 3. *Status of Patients With Cystadenocarcinoma of Pancreas Not Resected*

	Lesion					
Age, yr	Site	Size, cm	Grade	Treatment	Metastasis or local invasion	Follow-up
47	Tail	12	2	Partial excision	Invasion of lt kidney and transverse mesocolon	Dead, 2 yr, with metastasis
73	Tail	12	2	Partial excision	. . .	Dead, 1 yr
69	Head	5	2	Partial excision	Hepatic metastasis	Dead, 5 yr
65	Total pancreas	20	1	Biopsy and bypass	Hepatic metastasis	Dead, 3 mo
65	Head	Large	2	Biopsy*	. . .	Dead, 11 yr
69	Head	5	1	Biopsy	. . .	Dead, 2 wk
59	Head	Large	1	Biopsy	. . .	Dead, 6 mo

* Lesion attached to superior mesenteric vessels and inferior vena cava, precluding resection.

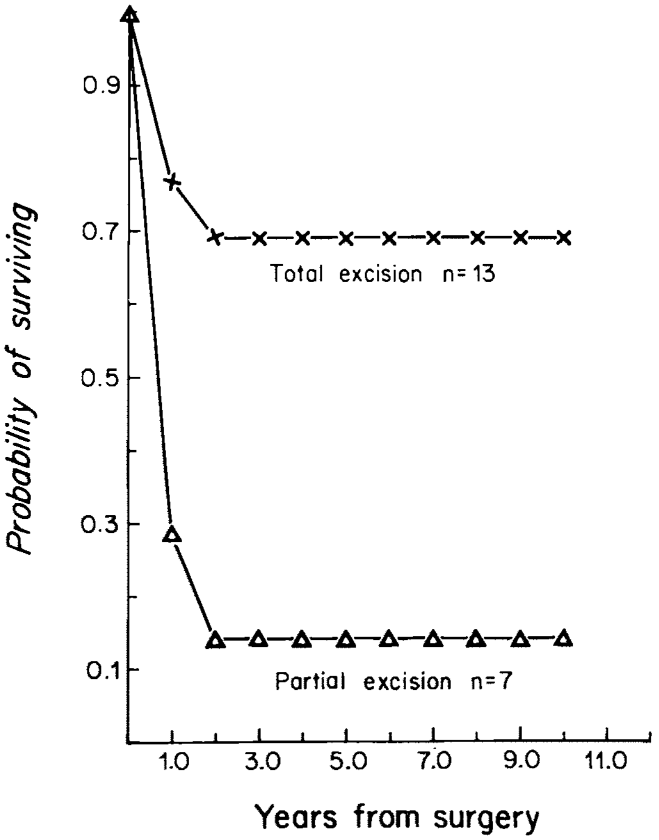

FIG. 4. Patient survival. Complete removal compared with incomplete removal.

procedure, three had total pancreatectomy, three had partial resection, one had a bypass, and three had biopsy. Detailed data on the patients who were not treated with resection are summarized in Table 3.

Results of Treatment

Follow-up data were collected from the time of surgery to death or current status in 1976. There were two postoperative deaths: one after biopsy and the other after a Whipple pancreaticoduodenectomy.

The five year survival for patients with grade 1 lesions was 64% and for those with grade 2, 24% (Fig. 3). For patients who had total excision of the tumor, the five-year survival was 68%, while for those who had partial and noncurative excision, the five year survival rate was 14% (Fig. 4).

Summary

Pancreatic cystadenocarcinoma is rare. Cystadenomas occur about twice as frequently as do cystadenocarcinomas. Eight patients with cystadenocarcinomas were surgically treated at the Mayo Clinic during the years 1963 through 1974, and 21 patients were treated surgically between 1928 and 1974. All had histologic features of benign mucous cystadenoma in portions of the cystic tumor wall. Most of the tumors were low-grade malignancies, and distribution was throughout the pancreas, although they were slightly more frequent in the head of the pancreas. Four patients had metastasis at initial surgery. Seven patients had tumors that were not treated with curative resection. For complete removal of the tumors, distal pancreatectomy, total pancreatectomy, or a Whipple pancreaticoduodenectomy is recommended. The five year survival rate after complete removal was 68%.

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Sequential Femoral-tibial Bypass Grafting for Limb Salvage

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Bypass grafting to distal lower extremity vessels continues to be associated with a high rate of graft occlusion. By utilizing a sequential side-to-side anastomosis between saphenous vein and popliteal artery in femoral-tibial bypass grafts, runoff can be increased and graft patency thereby improved. Sequential femoral-tibial grafts were employed in seven patients with gangrene, trophic changes, or restpain, all of whom had single-vessel runoff by arteriography. All seven sequential grafts established to a distal vessel in addition to the popliteal artery have remained open for periods of five to 27 months as determined by palpable graft or foot pulses. Two patients underwent below-knee amputation within six months of operation but had patent grafts at the time of amputation. In three patients ischemic ulcers resolved and in two patients toe amputations healed successfully. Sequential bypass grafting is a technique aimed at improving the patency rate of femoral-tibial bypass grafts by augmenting runoff.

PATIENTS WITH THREATENED LIMB-LOSS who are found to have advanced arteriosclerotic changes in the vessels distal to the popliteal trifurcation present a difficult problem in operative management. Poor runoff resulting in low flow rates through long grafts into small distal arteries augments the technical difficulty of constructing a durable reconstruction. For these reasons among others the patency rate of arterial reconstructions to the tibial and peroneal vessels is lower than that of femoropopliteal reconstructions and the consequent rate of limb loss is higher.[3-7,9-11,14] Nevertheless, bypass grafting to distal lower extremity vessels is an established technique in vascular surgery whose performance is justified as a limb salvage procedure.[1,3,15,16]

We have recently described a technique for increasing runoff by performing a side-to-side anastomosis to an isolated popliteal segment with the same vein that is used for the anastomosis to the single distal artery.[4] Seven consecutive patients have undergone femoral-tibial bypass grafting with such a sequential anastomosis to an isolated popliteal segment with resultant short-term graft patency in all.

Materials and Methods

Seven patients (ages 60–85) underwent femoral-tibial bypass grafts because of gangrene or trophic lesions (five patients) or rest pain with pregangrenous changes (two patients). Four were male and three were female. All but one were either diabetic or hypertensive, or both. All had advanced peripheral vascular disease and five had undergone previous aortofemoral reconstruction, lumbar sympathectomies, or amputation of the contralateral limb (Table 1).

All patients underwent arteriography with biplanar views and reactive hyperemia as necessary to delineate their distal vessels. All had superficial femoral and proximal popliteal artery occlusions with significant arteriosclerotic changes distal to the popliteal trifurcation so that only one distal vessel was considered suitable for grafting. Profundaplasty was not considered a feasible alternative in any of these patients. Patients were prepared for operation by treatment of diabetes and hypertension and vigorous attention to pulmonary toilette. Ischemic ulcers were treated with local measures, and with systemic antibiotics if cellulitis or inflammation was present. All patients were begun preoperatively on systemic antibiotics which were continued intra- and postoperatively.

At operation the single open distal vessel was exposed first to reconfirm its patency. The anterior tibial artery was exposed at its mid or distal third by a longitudinal incision between the tibia and fibula. Access to the posterior tibial artery was gained about 8 cm above the medial malleolus where it exits from under the lowermost fibers of the soleus. The popliteal artery was isolated and mobilized for construction of

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Reprint requests: Fredric Jarrett, M.D., University of Wisconsin Hospitals, Department of Surgery, 1300 University Avenue, Madison, Wisconsin 53706.

Submitted for publication: December 13, 1977.

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TABLE 1. *Summary of Clinical Information on Seven Patients*

Patient	Age	Sex	Diabetes	↑BP	Operative Indication	Previous Vascular Surgery	Result
1.	73	M	+	−	Restpain	Femoral poplateal bypass	Re-explored for thrombus at 24 hours Remains open—27 months
2.	67	F	+	−	Ulceration	None	Healed toe amp. Remains open—15 months
3.	70	F	−	+	Ulceration-heel	Embolectomy	Below-knee amp. at 1 month for sepsis Remains open—11 months
4.	70	F	−	+	Ulceration-heel	Lumbar sympathectomy	Healed ulceration Remains open—16 months
5.	85	M	−	−	Restpain	Lumbar sympathectomy	Restpain relieved Remains open—20 months
6.	83	M	+	+	Gangrene-toes	None	Healed toe amputation Remains open—12 months
7.	60	M	+	−	Ulceration-malleolus	Lumbar sympathectomy aorto-femoral graft	Poor healing of ulcers Below-knee amputation—5 months Died 13 months after operation

the side-to-side anastomosis. A sufficient length of saphenous vein was harvested from the ipsilateral limb and prepared for use as a bypass graft. One patient's vein was of insufficient length and a 6 mm Dacron® graft was utilized as the proximal portion of the composite graft. For anterior tibial anastomoses the vein graft was passed along the anterior tibial artery by enlarging the opening in the interosseous membrane and the distal popliteal artery was utilized for the sequential anastomosis. When grafting was performed to the distal posterior tibial artery a more proximal portion of the popliteal artery was preferred to allow less angulation of the vein graft. Tunnels were created and all patients were systemically heparinized. The distal arteries were occluded by traction with heavy ligatures rather than with clamps during construction of the distal anastomosis with a running 6-0 or 7-0 polypropylene (Prolene) suture. The vein graft was then passed proximally to lie alongside the popliteal artery, and a side-to-side anastomosis was performed with 6-0 polypropylene, followed by construction of the proximal anastomosis to the common femoral artery. If the vein graft was not of sufficient length to reach the common femoral, the proximal superficial femoral artery, if open, was utilized. All wounds were closed without drainage.

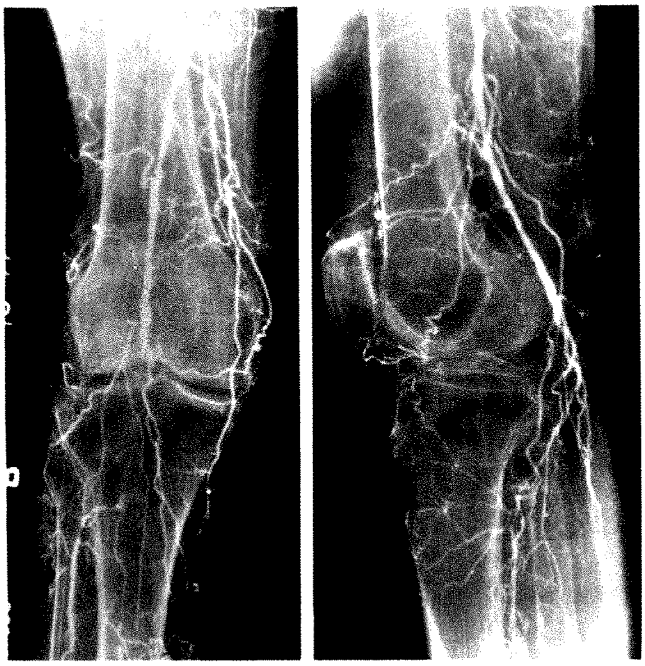
Results

All seven patients survived. The single composite Dacron-vein graft thrombosed in the immediate postoperative period and reexploration and thrombectomy were required to successfully re-establish flow. All seven grafts have remained open for periods of five to 27 months as determined by palpable graft or distal pulses. One patient underwent below-knee amputation because of an infected heel ulcer one month after grafting, but had an open graft at the time of amputation and ten months subsequently. Two patients successfully healed toe amputations after revascularization, and three additional patients healed ischemic ulcers after revascularization. The remaining patient required below knee amputation five months after grafting because of persistent ischemic ulceration involving tendon.

Discussion

Each advance in the technique of revascularization of lower extremity arteries has brought relief from the complications of ischemia to new groups of patients.[1,7,12] Bypass to vessels below the popliteal trifurcation has been successfully performed for several years to relieve ischemic lesions and distal gangrene. Short-term (30 day) patency has varied between 65–80%, and patency at one year between 40–76% in most series.[7,9–11,15] Modifications in technique are necessary to improve the patency rate of bypass grafts to small distal arteries. Reconstructions involving vessels in the distal third of the leg also potentially introduce the risk of non-healing of operative incisions if the reconstruction is unsuccessful.

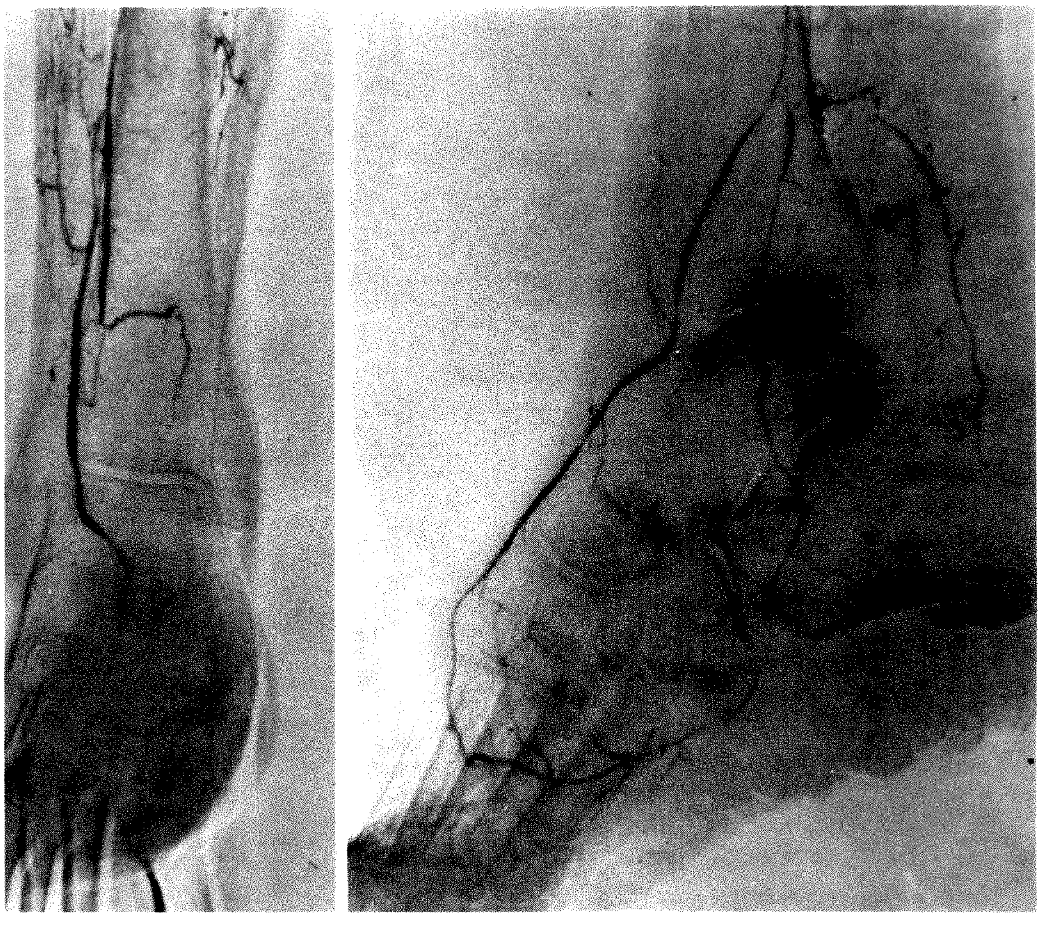
Patients with threatened limb loss from ischemic lower extremity lesions who have both superficial femoral artery occlusions and extensive distal disease are often considered poor candidates for arterial reconstruction and undergo amputation as an initial procedure. We have demanded complete arteriographic



FIGS. 1a and b. Anteroposterior and lateral views of an arteriogram showing occlusion of the popliteal artery with poor runoff to a small segment of the anterior tibial artery in its proximal portion.

evaluation with reactive hyperemia and biplane views before deciding a patient was not a suitable candidate for arterial reconstruction. Frequently patients who are deemed inoperable on the basis of severe occlusive disease at the popliteal trifurcation have at least one open tibial vessel in the distal leg which can be demonstrated with complete arteriograms (Figs. 1 and 2). When inflow is established to this vessel by a vein graft, collateral flow to the foot may improve, and vessels in the more proximal limb can fill in a retrograde manner as well. Adequate arteriographic demonstration of the distal arteries can obviate construction of an anastomosis proximal to an unrecognized partial occlusive lesion, and thereby eliminate a potential cause of graft occlusion.

Edwards and associates used multiple sequential grafting in several instances and reported encouraging results as compared with single femoral-tibial anastomoses.[6] They noted an additive effect on graft flow with the performance of additional anastomoses which they believe contributed to continued patency. We have not customarily obtained flow measurements in our patients because the anastomoses are performed from distal to proximal, and comparison of graft



FIGS. 2a and b. Anteroposterior and lateral subtraction views of the ankle and foot in the same patient showing filling of the distal arterior tibial artery through collaterals from the peroneal.

flow rates with and without the side-to-side anastomosis would involve multiple clamping of an arteriosclerotic popliteal artery, which we have been loathe to do. In one instance when flow measurements were obtained, there was an increase from 30 cc/min to 90 cc/min with opening of the side-to-side anastomosis. Several authors[2,5,9,13] have reported the use of sequential anastomoses for aortocoronary bypass. Grondin[8] reported a marked increase in blood flow of the proximal aortocoronary vein graft using this technique, and Bigelow[5] reported an arteriographic patency at three years which exceeded the figures using individual vein grafts.

Several technical points have been helpful. Whenever possible we have avoided placing vascular clamps on small distal arteries, and have preferred to use traction on a small polyethylene catheter for arterial occlusion while constructing the distal anastomoses. Coronary artery dilators (1.0–2.5 mm) have been useful in assuring patency of the distal artery as well as slightly dilating the vessel distal to the anastomosis. Magnification loops are used when necessary.

Femoral-tibial bypass has been performed by many surgeons as a limb salvage procedure. Early and late graft failure may be attributed to a number of factors including unrecognized disease distal to an anastomosis, progression of distal disease, technical errors, and inadequacy of the vein graft. In our estimation, a common reason for graft occlusion is inadequate runoff due to small, diseased distal vessels as well as the use of a long saphenous vein of small caliber. Any technical measures to improve runoff may be expected to improve both the short and long-term patency of femoral-tibial bypass grafts. We have utilized a technique for augmenting runoff by constructing a sequential side-to-side anastomosis between saphenous vein and popliteal artery. Short-term results in seven consecutive patients have been excellent. Additional follow-up will be necessary to evaluate the influence of this technique on long-term graft patency and limb salvage.

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The Stapled Gastrointestinal Tract Anastomosis:

Incidence of Postoperative Complications Compared with the Sutured Anastomosis

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Performance of gastrointestinal anastomosis by means of surgical stapling devices has achieved popularity in the last decade even though no detailed study has been reported comparing complications following the stapled anastomosis with those following hand sutured procedures performed by the same surgeons. We have reviewed 812 operative procedures on the gastrointestinal tract performed in one hospital over a four year period. Stapled anastomoses were performed in 472 with 13 (2.8%) complications related to the anastomosis; in 296 sutured anastomoses there were nine (3.0%) related complications. Comparison did not disclose any significant difference in the number of complications in these two groups. In 44 instances wherein the anastomosis contained both staples and sutures, there were no related complications. Further analysis of the patients in each group disclosed that stapling procedures were utilized in a much higher percentage of those operations which were performed under emergency conditions or in the presence of intra-abdominal sepsis, intestinal obstruction, and carcinomatosis. If the technical details of surgical stapling are mastered, this technique appears to be as safe as suturing in the performance of anastomoses in the gastrointestinal tract.

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ALTHOUGH THE FIRST CLINICALLY useful stapling device was developed by DePetz in 1927,[1] further progress was not remarkable until the early 1960's when the Institute for Experimental Apparatus and Instruments in Moscow developed a group of instruments capable of performing gastrointestinal tract anastomoses. Since these instruments were somewhat cumbersome and required that individual staples be inserted into the instrument by hand prior to each use, they did not receive widespread acceptance. Ravitch and his associates[6] were responsible for introducing a modified form of the Russian stapling device to this country. A great advance in the utility of the staplers was achieved with the development of instant loading with sterile cartridges each containing as many as 33 staples. Ravitch[7-9] also reported further studies in animals and humans and described techniques for the performance of gastrectomy as well as small bowel and colonic anastomoses.

It has been estimated on the basis of staple sales, that several hundred thousand operations using Autosuture stapling techniques were performed in the U.S.A. last year. Acceptance of staplers has largely bypassed the academic institutions where the necessity of teaching residents basic surgical techniques may have had a higher priority than study of the new technology.

Gritsman,[3] one of the pioneers in the development of the Russian stapling apparatus, in 1966 reported a collective series of 1,663 stapled gastric resections performed by a large number of surgeons in the USSR with a mortality rate of 2%. He compared these with a second series, which he collected from the world literature, of 52,886 gastrectomies done with suture technique by 62 surgeons with a mortality rate of 4.4%. Steichen and Ravitch[11] reported 147 of their own stapled gastrointestinal operations with 11 complications. Latimer and associates[4] studied 112 stapled operative procedures with a stapler-related complication rate of 1.9%. Lawson and associates[5] reported 122 operations on the alimentary canal done with stapling devices accompanied by a 4.0% complication rate. No study has yet been reported comparing complications following stapled anastomoses with those following hand-sutured procedures performed by the same group of surgeons. In an effort to shed light on the relative merits of these two techniques, the authors are reporting a study of this type with reference to 812 consecutive gastrointestinal procedures.

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Submitted for publication: December 27, 1977.

0003-4932/78/1100/0689 $00.90 © J. B. Lippincott Company

Material and Methods

By reviewing the operating room log book of the Booth Memorial Medical Center for the period between July 1, 1973 and June 30, 1977, the names and chart numbers of all patients having gastrointestinal operations were obtained. These charts were then reviewed to determine the nature of each operative procedure, the technique of anastomosis and any complications which may have occurred during the course of hospitalization.

Classification of Complications

Complications of anastomoses were grouped in three categories: 1) If an enterocutaneous fistula, leak, hemorrhage or obstruction occurred at the site of the anastomosis, this was obviously a "related" complication. Included also are cases of perianastomotic abscess and generalized peritonitis. 2) If the patient developed a subphrenic or pelvic abscess at a distance from the anastomosis with no direct contact, this was considered "possibly related," as was the development of intestinal obstruction due to adhesions not at the anastomotic site. 3) Complications were considered "unrelated" if the patient developed such conditions as myocardial infarction, atelectasis, cerebrovascular accident or pulmonary embolism. A study of comparative wound infection rates is not included in this report even though the technique selected for anastomosis might indeed have influenced the incidence of infection in the incision. The reason for this omission stems from the fact that skin wounds, contaminated by the intra-abdominal procedure, were either left open, sutured closed or drained according to the prejudices of the surgeon. Since there was no uniform pattern of wound management during the period under study, a statistical review of infected wounds as a "related" complication would prove meaningless.

Classification of Operative Procedures

Each gastrointestinal anastomosis was considered to be an operative procedure. Consequently, if a patient had both a small bowel resection with anastomosis and a colon resection with anastomosis, these were counted as two procedures. Bilroth II subtotal gastrectomy, for the purpose of this study, was classified as two procedures. 1) Duodenal stump closure and 2) gastroenterostomy. In this way it was possible to calculate the specific morbidity rate for each type of suture or staple procedure.

Anterior resections performed at or below the peritoneal reflection were classified as being done by suture if no staples were involved. These were all end-to-end anastomoses in this series. The Baker side-to-end colorectal anastomosis is a special case combining an everted stapled closure of the distal end of colon with suture anastomosis between the side of colon and the end of the rectal stump. In only two cases were low colorectal anastomoses done exclusively with staples. The new EEA stapling device, especially designed to perform this type of anastomosis, was not available during the time period of this study.

Surgical Technique

In each case the operative techniques were those described by Ravitch and Steichen[9] (Figs. 1–4). The everted stapled closures were not turned in with an additional layer of sutures in the cases included in this series. Ten attending surgeons and twelve surgical residents performed the operations, utilizing the Autosuture TA-55, TA-90, and GIA stapling devices. When anastomoses were performed by hand suturing, standard techniques were utilized. In most cases involving either the small bowel or colon, open anastomoses were constructed using fine catgut for the mucosa and interrupted nonabsorbable sutures for the seromuscular layer although occasionally a one layer technique was used.

Case Selection

All gastrointestinal anastomoses done during the period under study were reviewed. Six patients were rejected because they died of unrelated causes, such as myocardial infarction, stroke or pre-existing sepsis, so soon after operation as not to allow sufficient time to elapse for an anastomotic complication to become manifest. All other cases were included in the study. Whether staples or sutures were to be utilized in any case was a decision left entirely to the judgment or personal preference of the operating surgeon.

Technical Training

Although a course of instruction in surgical stapling given at the University of Pittsburgh was attended by the senior author, much of the staff's early training in the application of the stapling devices was provided by representatives of the manufacturer.

Adverse Factor Analysis

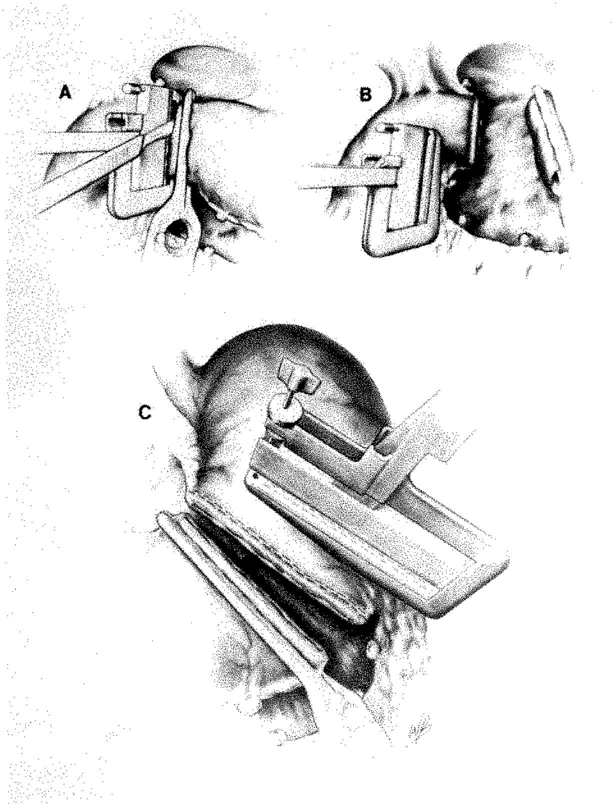
Since this is a retrospective study, it is possible that a disproportionate number of patients with conditions having an adverse effect on anastomotic healing might have accumulated in one of the two groups under study, thus jeopardizing the validity of the comparison. Consequently, seven categories of adverse factors were selected. 1) Emergent or urgent nature of the surgery. 2) Peritonitis, gastrointestinal perforation or intra-abdominal abscess. 3) Gangrenous intestine. 4) Gastric or intestinal obstruction. 5) Crohn's disease.

6) Carcinoma, localized. 7) Nonresectable carcinoma, liver metastases or peritoneal carcinomatosis.

Most surgeons would agree from their personal experience that these factors do have an adverse effect on anastomotic healing, and statistical validation for most of the above items is evident in the report by Schrock, Deveney and Dunphy.[10] Charts of patients included in this study were reviewed for the presence of any of the above adverse factors. The incidence rate of each adverse factor was calculated individually for the various suture and staple techniques. Not subjected to this adverse factor analysis were colostomy closures and anterior resections because these cases were not done under emergency conditions and few of the other adverse factors were operative.

Results

Mean age of all patients having sutured anastomoses was 62.5 years compared to 63.3 for stapled cases. Analysis of the specific mean ages for each of the sutured and of the stapled operative procedures under study did not disclose any clinically significant differences.



Figs. 1a–c. Technique of gastrectomy. (a) TA-55 stapled everting closure of duodenal stump. (b) Appearance of stapled duodenal stump. (c) TA-90 everted stapled closure of gastric pouch after division of stomach.

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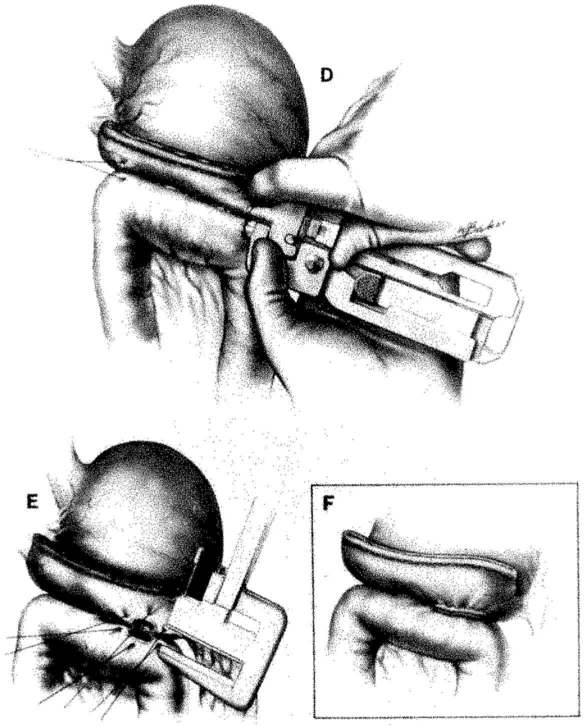

Figs. 1d–f. Insertion of GIA stapling device into stab wounds in the gastric pouch and proximal jejunum. This device, when fired, will accomplish an anastomosis between the posterior wall of the gastric pouch and the jejunum. (e) Residual defect in the anastomosis being prepared for stapled closure. (f) Completed gastrojejunostomy.

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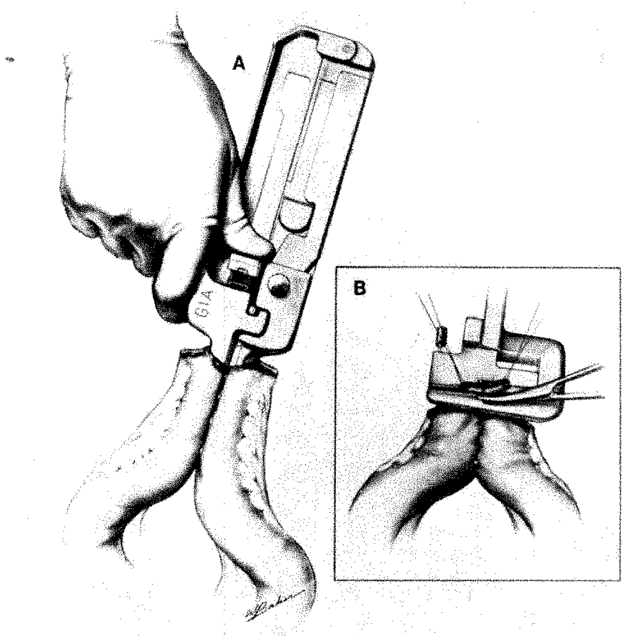
Table 1 summarizes the incidence of factors having an adverse effect on anastomotic healing. It is obvious that with the exception of Crohn's disease, each of the adverse factors were more prevalent in patients undergoing stapled procedures. For example, 24% or 438 stapled anastomoses were done under emergency conditions compared to 9% of sutured procedures. Carcinomatosis, gastric or intestinal obstruction, gangrene of bowel and infection were also more prevalent among the stapled cases.

Complications following each of the operative procedures under study are summarized in Table 2. There is no statistically significant difference in the incidence of "related" complications between the sutured and stapled groups when tested by the Chi-square method (3.0% vs. 2.8%). The same is true of the incidence of "possibly related" complications for the two groups (1.4% vs. 1.3%). It is interesting to note that of the 27 complications following those operative pro-



Figs. 2a and b. Technique of stapled small intestinal anastomosis. (a) Each segment of small intestine has previously undergone everted stapled closure, followed by excision of the antimesenteric corner of each segment. The GIA stapling device has been inserted and fired, completing a side-to-side anastomosis. (b) The residual defect in the stapled anastomosis is closed in an everting fashion by appling and firing the TA-55 stapling instrument.

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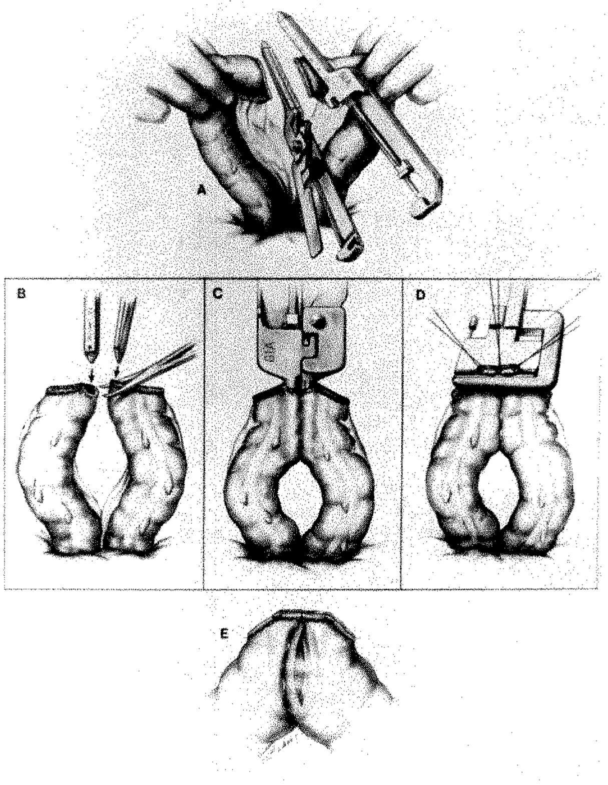
cedures of the types listed in Table 1, 22 occurred in patients having adverse factors. All of the complications are described in Tables 3–10.

As will be evident from perusal of Tables 3–10, it is often difficult to ascertain whether a complication was related to the healing anastomosis or whether it was an inevitable result of the pathological process for which the operation was performed. In questionable cases the complications were included in our statistics as "possibly related."

Discussion

The incidence of anastomotic complications (Table 2) following stapled procedures was so nearly identical with that following hand-sutured operations as to be startling. Review of the data in Table 1 indicates that if there is any bias in this retrospective study, it heavily favors the sutured procedures. A much higher proportion of acutely ill patients undergoing emergency surgery had their anastomoses performed by the stapling technique in order to save operating time. Patients suffering from abdominal abscess, peritonitis, gangrenous bowel, intestinal obstruction and peritoneal carcinomatosis underwent anastomoses by stapling far more frequently than by suturing. With respect to cases of small intestinal obstruction undergoing resection and anastomosis, of the 28 cases in this series, 25 were anastomosed with staples; of 22 with strangulation of small bowel, 21 had stapled procedures. It is notable that 69% of all 32 anastomotic complications occurred in patients with one or more adverse factors.

Schrock, and associates[10] demonstrated a marked increase in the incidence of clinically apparent anastomotic leakage following ileocolonic and colonic resections if the operations were done under emergency conditions or were accompanied by bacterial or fecal contamination, operative hemorrhage or shock.



Figs. 3a–e. Technique of stapled colonic anastomosis. (a) GIA instrument has just completed simultaneous division of colon with stapled everted closure of proximal and distal segments. (b) Openings are made into the proximal and distal segments of colon by excising the antimesenteric corner of each segment with scissors. (c) The GIA stapling device is inserted and a side-to-side anastomosis between the two limbs of bowel is accomplished. (d) The residual defect is closed with the TA-55 stapler. (e) Appearance of completed "functional end-to-end" colocolostomy.

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For example, when peritonitis, abscesses or fistulae were encountered at operation, anastomoses leaked in 10.5% of cases, compared to 3.7% in the absence of infection. Emergent cases exhibited an 8.2% leak rate. Even the presence of a localized colonic carcinoma resulted in a rate of clinical leakage twice that of operations performed for benign disease. Our study tends to confirm their findings with respect to both sutured and stapled anastomoses. Crohn's disease is included in our list of adverse factors due to the fact that most of our patients undergoing surgery for this condition had sustained one of the complications of the disease which produced some variety of intraperitoneal infection.

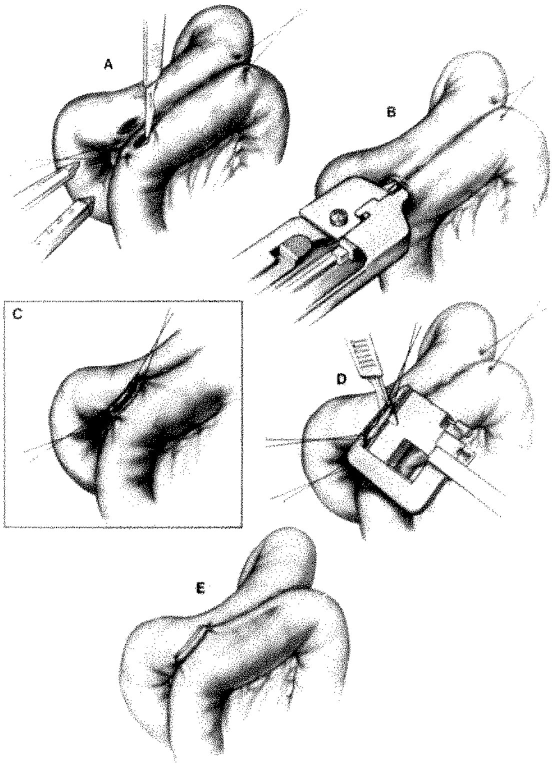
Although the procedure of right hemicolectomy with primary anastomosis has a reputation for successful healing even when performed under unfavorable conditions, Table 5 demonstrates that a number of anastomotic complications occurred following ileocolectomy performed in the presence of carcinomatosis, intestinal necrosis, peritonitis or abscess. Welch and Donaldson[12] noted a high mortality (18%) when right colectomy with anastomosis was performed for acute colonic obstruction, while Dutton and associates[2] found that 36% of their patients died following emergency resection and anastomosis of the obstructed right colon.

In one patient a pelvic abscess followed subtotal colectomy and ileosigmoid stapled anastomosis done for an acutely obstructing carcinoma of the left colon. This is considered by the authors to be a case of poor surgical judgment as results with preliminary colostomy followed by staged resection for left colon obstruction have been superior to one stage resection.[2,12] In our series, closure of colostomy resulted in no deaths and only a three per cent incidence of anastomotic complications.

Three cases of subhepatic or subphrenic abscess, cited in Table 3, followed gastrectomy either for carcinoma or obstruction. In each of these cases it is considered highly improbable that the infection resulted from any leak at the site of the gastrojejunostomy. Rather, contamination by virulent organisms present in the stomach appears to be the likely cause of these infections.

In the case of the postoperative gastric hemorrhage following a stapled gastrojejunostomy, this was considered to be a technical error. Performed early in our experience with stapling techniques, inadequate attention was paid to the oozing of blood from the gastrojejunal staple line. It is now known that it is imperative to correct this bleeding by means of electrocoagulation or suture ligation.

In reviewing duodenal stump closure it is notable that two of the five leaks occurred in patients with gastric carcinoma in whom the duodenum appeared to be free of pathology. The only fatal duodenal complication occurred in a patient in shock undergoing emergency gastrectomy for massive hemorrhage from a large posterior penetrating duodenal ulcer, in whom the precaution was taken of performing a tube duodenostomy at the time of gastrectomy. This was not successful in preventing duodenal fistula and peritonitis. In two stapled duodenal closures, minor leaks appeared along the drain tracts. In one patient, who was discharged from the hospital healed, a duodenal fistula occurred on the twenty-first postoperative day along the drain tract. Another patient with a duodenal leak following stapled closure underwent reoperation on the fourth postoperative day. No gross leak could be seen, but drains were inserted and the fistula persisted for three weeks. This complication was considered due to a technical error in that the duodenal stump was excessively scarred making it too thick for



FIGS. 4a–e. Technique of stapled side-to-side jejunojunostomy. (a) After aligning the two segments of jejunum, stab wounds are made at the antimesenteric borders of each segment. (b) GIA instrument is inserted, one fork in each lumen. Firing the instrument will result in side-to-side anastomosis. (c) Residual defect in anastomosis, resulting from stab wounds. (d) Residual defect has been closed in an everting fashion utilizing the TA-55 stapler. (e) Appearance of completed anastomosis.

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TABLE 1. *Incidence of Factors with Adverse Effect on Anastomotic Healing*

	No.	Operations Nonelective	Perforation or Pus	Bowel Gangrene	Obstruction	Crohn's Disease	Carcinoma	Nonresectable CA or Metastases
Gastrojejunal								
sutured	32	19%	3%	0	26%	0	29%	23%
stapled	111	22%	5%	0	18%	1%	35%	24%
Duodenal stump								
sutured	31	13%	0	0	*	0	13%	3%
stapled	68	28%	6%	0	*	0	29%	3%
Ileocolonic								
sutured	57	7%	7%	5%	7%	14%	67%	9%
stapled	85	21%	20%	6%	15%	11%	71%	12%
Colocolonic								
sutured	71	6%	8%	4%	1%	1%	54%	8%
stapled	61	8%	8%	0	2%	2%	63%	33%
Small intestine								
sutured	30	30%	6%	3%	10%	0	30%	30%
stapled	106	39%	18%	20%	24%	3%	42%	27%
Esophagogastric								
sutured	4	0	0	0	0	0	100%	25%
stapled	6	0	0	0	0	0	100%	33%
Total								
sutured	224	9%	6%	3%	7%	4%	46%	13%
stapled	438	24%	11%	6%	14%	3%	47%	21%

* Not relevant.

TABLE 2. *Complications Following Sutured and Stapled Operative Procedures*

		Complications	
	No.	Related	Possibly Related
Gastrojejunostomy			
sutured	32	0	1 (3%)
stapled	111	1 (1%)	3 (3%)
Duodenal stump closure			
sutured	31	2 (6%)	0
stapled	68	3 (4%)	0
Ileocolonic			
sutured	57	3 (5%)	2 (4%)
stapled	85	3 (4%)	2 (2%)
Colocolonic			
sutured	71	0	1 (1%)
stapled	61	0	0
Small intestine			
sutured	30	1 (3%)	0
stapled	105	4 (4%)	1 (1%)
Closure colostomy			
sutured	33	0	0
stapled	33	2 (6%)	0
Esophagogastric			
sutured	4	0	0
stapled	6	0	0
Anterior resection			
sutured	38	3 (8%)	0
Baker	44	0	0
stapled	2	0	0
Total			
sutured	296	9 (3.0%)	4 (1.4%)
stapled	472	13 (2.8%)	6 (1.3%)
Baker	44	0	0
Total	812		

proper closure by stapling. Since the stapling device will compress tissues to a thickness of 1 to 1.5 mm when using the 3.5 mm staple, it is important to remember that no tissue which may be necrotized by this degree of compression should be stapled. Vital to the success of any stapled closure is the viability of the tissue distal to the staple line. Stapling is not equivalent to a completely hemostatic ligature. One can uniformly observe a brief period of gentle oozing through the stapled closure. When tissue is too thick for this to occur, the technique is contraindicated. Some leeway in this area may be obtained by using the larger 4.8 mm staple, which will permit the closure of moderately thickened tissue. With the use of the

TABLE 3. *Complications Following Gastrojejunostomy*

- Sutured (32)
  - Related—(0)
  - Possibly related—(1)
    - Subhepatic abscess after gastrectomy for obstructing ulcer; relap
- Stapled (111)
  - Related—(1)
    - Postoperative gastric hemorrhage, three units; no relap; *technical error*
  - Possibly related—(3)
    - Subhepatic abscess after gastrectomy for carcinoma; relap;
    - Subhepatic abscess after gastrectomy for carcinoma of residual gastric pouch; relap
    - Obstruction due to fibrosis at efferent stoma after gastrojejunostomy for Crohn's duodenitis; relap

TABLE 4. *Complications Following Closure of Duodenal Stump*

- Sutured (31)
  - Related—(2)
    - Duodenal fistula after gastrectomy for carcinoma; healed without relap
    - Duodenal leak and peritonitis following suture closure of duodenum and tube duodenostomy during emergency gastrectomy for massive hemorrhage—fatal
- Stapled (68)
  - Related—(3)
    - Duodenal fistula healed in four weeks—minor; no relap
    - Duodenal fistula along drain tract following gastrectomy for carcinoma appeared on p.o. 22, after discharge from hospital; healed in three weeks—minor; no relap
    - Duodenal leak; reoperation p.o. 4 to insert tube duodenostomy; healed in two weeks; *technical error*—stump too thick for stapled technique

larger staple, the tissue compression may be adjusted to a 2–2.4 mm thickness.

One of the technical failures following a stapled anastomosis occurred in a patient with a strangulating inguinal hernia requiring resection of the patient's ileum. The resection and anastomosis was carried out in the inguinal incision after which the anastomosed segment was pushed through the fairly narrow hernial ring into the abdominal cavity. This complication was attributed to the technical error of applying excessive force to a fresh anastomosis. Another technical error was responsible for a large fecal fistula which followed stapled anastomosis for closure of a transverse colostomy. The operation was performed through a small incision with inadequate mobilization of colon from adjacent adhesions. This resulted in excessive tension on the stapled closure with consequent leakage.

Needless to say, in an indeterminate number of additional cases, technical errors were detected and corrected during the course of stapling. Of course, this is also true of suture techniques, but surgeons spend five years in a residency program learning all the pitfalls of hand suturing. By contrast, the radically different technique of stapling is frequently applied with minimal preceptorship. Upon the completion of any stapling procedure, it behooves the surgeon to examine the entire anastomosis with meticulous care to seek out any possible imperfections. In the case of gastrojejunal anastomoses with the GIA device, complete hemostasis must be assured prior to completion of the procedure.

In our earlier application of stapled anastomoses to the small intestine, the authors felt some apprehension that the everted staple line might give rise to postoperative adhesions due to the rim of exposed mucosa. It was gratifying to observe that during the

TABLE 5. *Complications Following Ileocolonic Resection and Anastomosis*

- Sutured (57)
  - Related—(3)
    - Perianastomotic abscess after palliative right colectomy in 75 year old patient with carcinomatosis; relap. p.o. 10.
    - Obstruction, inflammation at anastomosis; relap. for bypass p.o. 15 (probable leak)
    - Death p.o. 11 of 90 year old following resection and jejunocaecostomy for gangrene of ileum; febrile p.o. course; no autopsy (suspected leak)
  - Possibly related—(2)
    - Recurrent pelvic abscess after resection for perforated Crohn's ileitis with pelvic abscess and peritonitis; relap. p.o. 11.
    - Transient small bowel obstruction in patient with peritoneal metastases; Cantor tube
- Stapled (85)
  - Related—(3)
    - Leak and peritonitis after subtotal colectomy and ileosigmoidostomy for Crohn's colitis; relap. p.o. 8.
    - Subhepatic abscess adjoining anastomosis; patient readmitted for I. & D. p.o. 26
    - Obstruction due to kink, adhesions and small abscess at anastomosis in 90 year old; probable leak; relap. p.o. 9
  - Possibly related—(2)
    - Small pelvic abscess noted at relap. for intestinal obstruction 15 days after emergency subtotal colectomy and ileosigmoid anastomosis for acutely obstructing carcinoma of left colon.
    - RUQ abscess and infected ascites after resection right colon for necrotic tumor with peritoneal carcinomatosis; relap. p.o. 3. Died of pulmonary emboli p.o. 12

TABLE 6. *Complications Following Colon Resection and Colocolonic Anastomosis*

- Sutured (71)
  - Related—(0)
  - Possibly related—(1)
    - Postoperative small bowel obstruction successfully treated by Cantor tube
- Stapled (61)
  - No anastomotic complications

TABLE 7. *Complications Following Small Intestinal Anastomoses*

- Sutured (30)
  - Related—(1)
    - Enterocutaneous fistula, 12 days duration, after side-to-side ileosigmoidostomy for carcinomatosis with obstruction
- Stapled (105)
  - Related—(4)
    - Leak following operation for strangulated hernia; resection done in groin and anastomosis forcibly reduced into abdominal cavity via hernial opening; relap. p.o. 7; *technical error*.
    - Enterocutaneous fistula following resection and anastomosis of multiple segments of small bowel for strangulating intestinal obstruction and abdominal abscesses, 10 days after hysterectomy; healed on hyperalimentation.
    - Enterocutaneous fistula following 2 small intestinal resections, sigmoid resection and drainage of abscesses for Crohn's enterocolitis and peritonitis; died—sepsis.
    - Enterocutaneous fistula following small bowel resection and resection enterovesical fistula in 71 year old with carcinomatosis and obstruction; died of sepsis
  - Possibly related—(1)
    - Relaparatomy, enterolysis for adhesive small bowel obstruction 30 days after resection of jejunal angiodysplasia; no leak

TABLE 8. *Complications Following Colostomy Closure*

- Sutured (33)
  - No anastomotic complications
- Stapled (33)
  - Related—(2)
    - Obstruction; perianastomotic inflammation; re-resection p.o. 14.
    - Fecal fistula; stapled anastomosis constructed under tension; *technical error*

four year period of this study no patient has returned with intestinal obstruction due to an adhesion involving one of these everted lines of staples. Since the period of observation is a brief one, some degree of apprehension remains and it may be advisable, when convenient, to cover the everted mucosa with adjacent mesentery or omentum.

Among the 32 complications related to anastomotic healing listed in Tables 3–10, there were only four fatalities from sepsis. This low rate is considered to be due to the emphasis in this institution upon prompt relaparotomy in all cases suspected of having anastomotic leakage. In these situations the anastomosis is generally divided and both limbs of intestine are exteriorized either as enterostomy or colostomy and mucous fistula.

The satisfactory results following stapling procedures in this series were not due to the efforts of a single experienced and skillful surgeon, but rather of a large number of staff surgeons and residents. It should be noted, however, that acquisition of experience and skill with these instruments was achieved in a gradual, organized fashion. No one inexperienced in the stapling technique performed an anastomosis without a preceptor being part of the operating team. Despite its apparent simplicity, there are just as many pitfalls to be avoided in learning stapling techniques as there are in learning how to sew. Once this technique is mastered, there appears to be no significant difference in results, comparing stapled and sutured anastomoses. Since the average stapled anastomosis takes no more than two to three minutes to perform, one reason for the increasing popularity of stapling is readily apparent. At present, approximately 60% of anastomoses in our institution are done with stapling techniques. They are particularly appropriate in critically ill patients in whom curtailment of operating and anesthesia time may be important.

TABLE 9. *Complications Following Esophagogastrostomy*

- Sutured (4)
  - No anastomotic complications
- Stapled (5)
  - No anastomotic complications

TABLE 10. *Complications Following Anterior Resection of Rectum*

- Sutured (38)
  - Related (3)
    - Perianastomotic abscess; drained transrectally.
    - Fecal fistula; conservative treatment.
    - Localized leak in patient with gauze pack in place for 3 days due to presacral hemorrhage. No relap
- Sutured and Stapled (Baker side-to-end) (44)
  - No anastomotic complications
- Stapled (2)
  - No anastomotic complications

In conclusion, data presented in this study do not show any significant difference in the incidence of anastomotic complications when stapled anastomoses are compared with sutured procedures in the gastrointestinal tract.

Acknowledgment

The authors wish to express their gratitude to Dr. Frank C. Spencer for his support and criticism.

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Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

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staphylococcal strains which are resistant to these penicillins.

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Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

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As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

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Safety for use in pregnancy has not been est

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The concurrent systemic use of other ototoxic and/or nephrotoxic drugs, particularly streptomycin, polymyxin B, polymyxin E (colistin), neomycin, gentamicin, and viomycin should be avoided.

The administration of kanamycin sulfate and rapid acting diuretic agents, e.g. ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, and mannitol (particularly when the diuretic is given intravenously) may cause irreversible deafness. Concurrent use of these agents should be avoided. (See "Adverse Reactions".)

Usage in Pregnancy

Safety of this drug in human pregnancy has not been established.

CONTRAINDICATIONS:

A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other potentially ototoxic agents may be a contraindication if effective, alternative therapy is available.

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(continued from page 75A)

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JAMES A. O'NEILL, JR., M.D.

Anesthesia and the Kidney. R. Dennis Bastron and Stanley Deutsch. 98 pp. New York, Grune and Stratton. 1976. $11.00.

THIS SECOND VOLUME in the series, "The Scientific Basis of Clinical Anesthesia," *Anesthesia and the Kidney*, brings together, in a wholly satisfactory manner, the available information. A small volume of eight chapters, it reflects, as the authors state, the paucity of work on the effects of Anesthetics on the Kidney. The bibliography is especially useful. The presentation is clear, orderly, almost spare. More than a third of the book is devoted to a concise review of renal physiology coupled with a clear clinical evaluation of renal function. Of special interest are the chapters devoted to the anesthetic management of the Anephric Patient and Diuretics. The chapter on nephrotoxicity of anesthetics is almost wholly concerned with an assessment of the problem of methoxyflurane toxicity. Discussion of other agents is dismissed with "all anesthetics are nephrotoxic in that they depress renal hemodynamics and function." For completeness one would have liked a more extended review of the effects of other agents. The delineation of the high renal risk in patients with obstructive jaundice, major vascular surgical procedure and hypotension, especially as these relate to the development of acute renal failure, is well done.

This book is easy to read and the arguments readily followed. The admonition to keep urine flowing at rates between 50–100 ml/hr during operation is like a beacon. The simple, straightforward presentation leads to an understanding and evaluation of renal function with appropriate admonitions necessary to chart a safe journey for the anesthetized patient. A more extensive discussion of the role of renin-angiotensin system would have been welcomed by this reviewer. The authors have indeed brought together the "core" of information regarding the kidney and anesthesia simply, unpretentiously, and effectively.

This volume will be most useful to all those desiring more information in this neglected area.

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Intestinal Bypass

A Modification

GENE B. STARKLOFF, M.D., JOSEPH C. STOTHERT, M.D., MURALI SUNDARAM, M.D.

Six hundred sixty-four patients who have had metabolic intestinal surgery for the treatment of morbid obesity are reviewed. Particular attention is directed to difference in weight loss, morbidity and mortality in end-to-side and end-to-end shunts, the former performed in 300 patients and the latter in 262 patients. Unsatisfactory weight loss was observed in 20% of patients with end-to-side shunts, while only 8% of patients with end-to-end shunts failed to lose a sufficient amount of weight. Morbidity and mortality were significantly increased in this latter group. This led to adoption of a modification of the end-to-side operation by developing a plication to prevent reflux. Our preliminary observation indicates that in 102 patients who have had this operation, similar weight loss is attained to that of end-to-end shunts with no greater morbidity or mortality than the end-to-side type.

From the Department of Surgery,
St. Louis University, St. Louis, Missouri

EARLY CONCEPT OF INTESTINAL short circuiting operation for morbid obesity[1,2] has gradually progressed to the currently accepted procedures of Payne[3] or Scott.[4] The modification of Scott came as a consequence of insufficient weight loss in certain patients who had undergone the end-to-side type of shunt. A number of theories existed as to the reason for this. Several authors felt that reflux of intestinal contents into the defunctionalized ileum resulted in increased absorption of nutrients and hence decreased weight loss.[5-7] Others believed that increased absorption developed in the shortened segment resulting in failure to lose sufficient weight. Further experience has shown that when the defunctionalized segment is removed from gastrointestinal continuity by conversion of end-to-side to end-to-end shunt additional weight is lost. The concept of reflux is, therefore, a valid cause of insufficient weight loss in most patients. Elimination of reflux should increase the degree of weight loss since this is the only essential difference between the end-to-side and the end-to-end type of shunt. Our experience with 664 patients, 102 of whom have had end-to-side shunts utilizing a modification which eliminates reflux, has resulted in similar weight loss to that occurring in comparable patients who have had end-to-end bypasses.

Material

Our choice of operation in the mobidly obese patient has changed through the years. Initially in the 1970–1973 period, we performed the Payne Shunt, an end-to-side jejunoileal anastomosis incorporating 36.6 cm of jejunum to 10.2 cm of ileum. On studying these first 300 patients, we were dissatisfied with the decrement of weight loss. If the patient's ideal weight was calculated and we arbitrarily placed any patient within 22.6 kg (50 lbs) as having a satisfactory result, 64 or 21% of our patients' loss would be judged as unsatisfactory.

While results were frequently satisfactory as far as other physiologic parameters, such as reduction in blood pressure, reduction in fasting glucose and cholesterol were concerned; most patients measured success primarily by the amount of weight loss. Therefore, about 20% of the patients were dissatisfied with the results of their operation. On evaluation of these patients, 95% were noted to have reflux of contents into the defunctionalized segment. Because of the insufficient weight loss, in October 1973 we began to do end-to-end jejunoileostomy with an ileo-colostomy as described by Scott. We used 30.5 cm of jejunum anastomosed to 23.3 cm of ileum on 262 patients. Our results with this group, in regard to return to ideal weight, were most gratifying. Only 21 patients, or 8%, failed to reach their ideal weight within 22.6 kg. During this period we converted 11 patients from end-

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Submitted for publication: January 10, 1978.

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TABLE 1. *Conversion of Payne to Scott Shunt*

Case #	Original Weight (kg)	Weight at Conversion (kg)	Interval Between Operation	Interval Since Conversion	Present Weight (kg)
1	143.18	109.09	2 years	2 years	77.27
2	143.18	122.79	3 years	2 years	76.81
3	152.72	90.90	1.5 years	1.5 years	65.90
4	177.27	109.01	2.5 years	2.5 years	81.81
5	120.45	99.54	3 years	1 year	86.36
6	144.09	144.09	1 year	1 year	85.90
7	163.18	145.90	3 years	1 year	122.72
8	132.72	90.90	1 year	4 years	67.27
9	168.18	136.36	3.5 years	.5 years	129.54
10	130.90	105.45	2 years	.5 years	97.27
11	126.36	103.63	1 year	2 years	85.0

to-side type to an end-to-end shunt. Table 1 gives the statistics as far as further weight loss following the conversion operation. As noted, further weight reduction has occurred and is continuing at an encouraging rate in most patients.

The greater weight loss in the end-to-end shunt patients was accompanied by a higher morbidity and mortality.[8] Table 2 depicts the mortality seen between our two types of shunts. A more significant rise in mortality was observed with the end-to-end group (8.0%) than the end-to-side group (2.7%). Both types of bypass procedures were evaluated as to intrinsic differences. No difference was found in age, weight, or secondary disease processes. We concluded the type of bypass procedure to be the main difference. It seems logical to assume that two bowel anastomoses would result in a higher complication rate than a single anastomosis, particularly if one anastomosis involved the colon. This led us to search for a procedure which would give us the weight loss of the end-to-end procedure and the reduced complication rate of the end-to-side anastomosis.

TABLE 2. *Mortality: End-to-End vs. End-to-Side Shunts*

Cause	262 End-to-End (Scott)	300 End-to-Side (Payne)
1. Anastomotic leak	4	0
2. Electrolyte abnormality	1	1
3. Pulmonary embolism	3	2
4. Hepatic failure	6	2
5. Pneumonia	0	1
6. Myocardial infarction	0	1
7. Aspiration	3	0
8. Hypoxia	1	0
9. Necrotising enterocolitis	1	0
10. Tuberculosis	1	0
11. Unknown	1	1
Total	21	8
Per cent	8.0%	2.7%

Description of Modification

As has been previously described, the essential difference between the two procedures is the handling of the bypassed segment of bowel. A method of prevention of reflux seemed to be the answer. A surgical maneuver was devised in which the antimesenteric border of the ileum just proximal to the end-to-side jejunoileostomy was attached to the antimesenteric border of the proximal (functional) jejunum for approximately 16 cm. This maneuver which does not involve an open anastomosis prevents reflux into the proximal ileum by one of two possible mechanisms. By plicating the proximal ileum to the functional jejunal segment reflux may be prevented by keep-

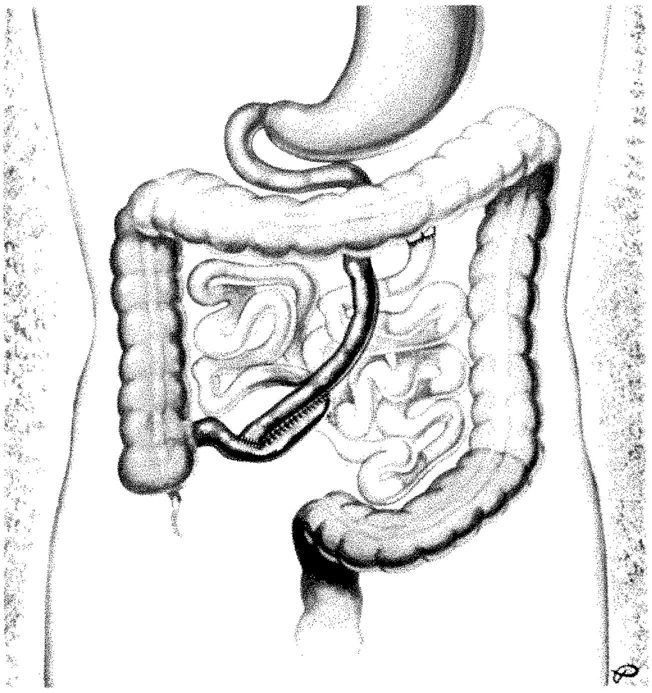

FIG. 1. A modification of the Payne shunt. Notice how the proximal ileum is tacked up to the distal aspect of the functional jejunum.

ing the defunctionalized ileum in a nondependent position, thus preventing reflux of chyme by gravity. A second possibility is that this procedure results in a partial obstruction to the reflux of chyme into the defunctionalized ileum. If this is the case the blind loop proximal ileum and distal jejunum formed would have to reach equilibrium or a closed loop obstruction (which has not occurred) would be the result. Figure 1 illustrates this procedure. The distal jejunal segment which is defunctionalized is oversewn and tacked to the mesentary of the transverse colon to prevent intussusception.[9]

Without this modification procedure, 60% of contrast studies reveal reflux into the bypassed segment in patients with end-to-side shunts. It was felt that the 40% who did not show reflux possibly had modified themselves by formation of adhesions. It has been our observation that those patients with the greatest amount of reflux lost the least amount of weight.

Discussion

The isoperistaltic end-to-side shunt with the described modification has been employed in 102 patients during the past 18 months. In two patients we have had the opportunity to reoperate on them for other reasons following the Payne Shunt. Prior to repair of a ventral hernia, a patient with less than 26 kg weight loss (after a Payne procedure) was subjected to a barium study of the gastrointestinal tract (Fig. 2). Reflux is noted in the defunctionalized segment. During repair of the hernia the abdominal cavity was entered and the modification was performed. Postoperatively a repeat barium study was performed (Fig. 3) and reflux has been completely eliminated; subsequently she has continued to lose weight. A second patient had similar x-rays and a similar result following modification.

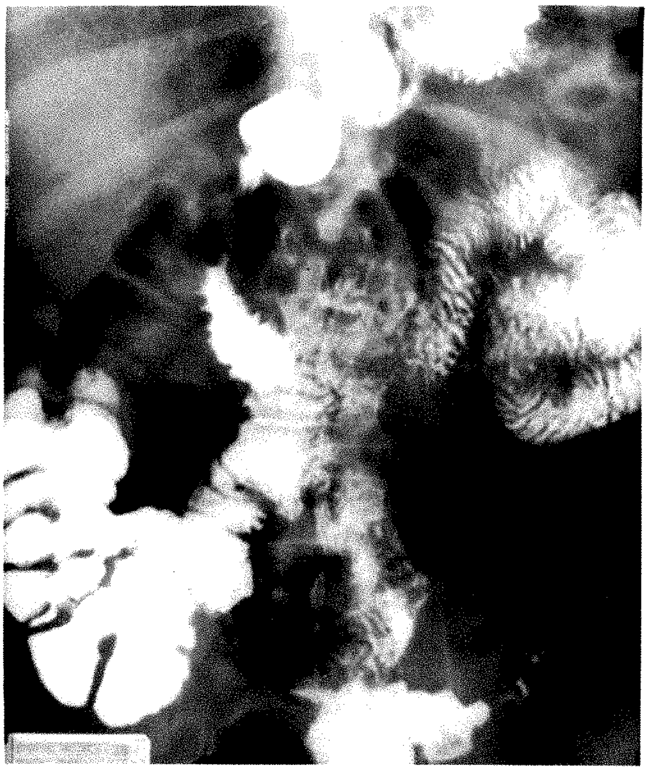

FIG. 2. Reflux in a patient with a previous Payne shunt without modification.

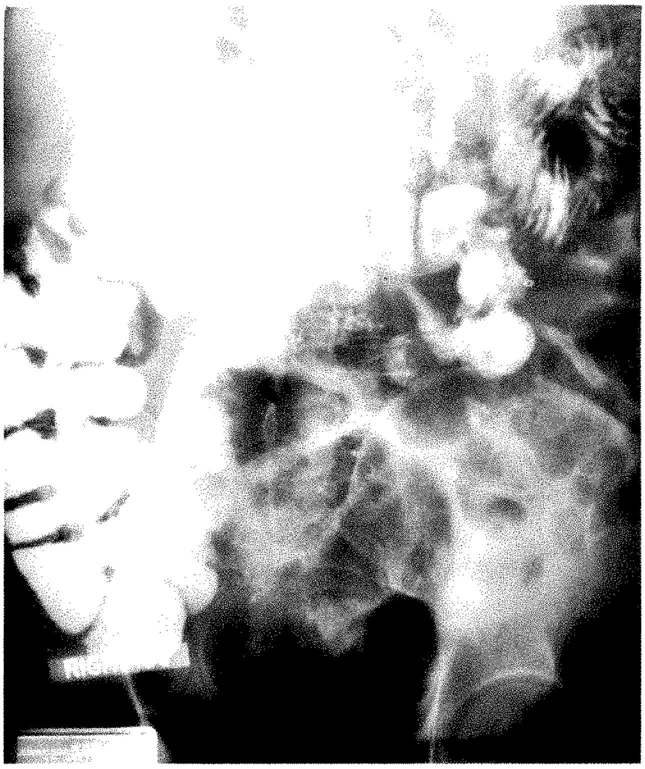

FIG. 3. The same patient after our modification. Notice the lack of reflux.

While it is much too early to critically evaluate weight loss with our modification, we have compared the results in ten consecutive patients to randomly selected end-to-end shunts, matched as equally as possible to age, height and weight. The modified shunts have been followed closely for one year. The randomly matched groups are shown in Table 3. The overall weight loss difference between groups A and B is not statistically different, although individual variation is present.

Summary

Our experience with end-to-side and end-to-end shunts in relation to weight loss, morbidity and mortality has been described. End-to-side shunts were

TABLE 3. *Weight Loss: Scott Shunt vs. Payne with Modification (kg)*

			Weight					
Case	Age	Ht.	Preop	2 mo.	4 mo.	8 mo.	1 yr.	Total Lost
1 A	36	5'9"	136.81	111.8	100.90	87.72	69.09	67.72
B	42	5'9"	141.36	—	114.54	100.90	91.36	50.0
2 A	29	5'5"	118.63	—	95.90	90.0	77.27	41.36
B	26	5'5"	120.45	105.0	99.54	90.0	75.0	45.45
3 A	30	5'2"	120.45	115.45	101.36	92.72	72.72	47.73
B	33	5'3"	145.0	—	117.72	88.63	76.36	68.64
4 A	23	5'5"	131.36	114.90	108.18	102.72	95.90	35.46
B	23	5'4"	122.27	110.0	99.09	75.45	63.63	58.64
5 A	43	5'8"	128.63	113.63	103.63	101.81	94.09	34.54
B	42	5'6"	125.0	116.36	110.45	98.63	91.81	33.19
6 A	42	5'4"	107.72	96.36	79.54	—	60.90	46.82
B	45	5'6"	111.81	83.63	83.18	74.09	63.63	48.18
7 A	29	5'6"	120.90	105.90	99.09	92.72	85.45	35.45
B	31	5'4"	120.0	—	89.54	77.27	73.18	46.82
8 A	45	5'3"	115.45	98.18	93.18	90.45	86.36	29.09
B	46	5'8"	111.36	109.09	98.63	87.72	85.90	25.46
9 A	26	5'7"	127.27	118.18	110.90	101.81	97.72	29.55
B	32	5'5"	123.18	—	106.36	99.54	94.09	29.09
10 A	30	5'4"	110.90	142.72	136.81	128.18	109.09	51.81
B	37	5'4"	155.0	125.45	116.36	—	84.54	70.46
Total wt. loss Scott's shunt								*475.93*
Total wt. loss Payne shunt with modification								*419.53*

A: Payne with modification. B: randomly matched Scott shunt.

unsatisfactory due to insufficient weight loss. End-to-end shunts produced satisfactory weight loss, but a significantly higher morbidity and mortality. Revision operations have consisted of conversion of end-to-side shunts to end-to-end shunts. While weight loss has been satisfactory, morbidity can be anticipated to develop due to the addition of the colonic anastomosis.

Our modification which is currently under evaluation incorporates the benefits of both procedures. With only one anastomosis, the morbidity is to be expected to parallel that of the Payne procedure. With the prevention of reflux we hope to find the amount of weight loss to be similar to the Scott Shunt. As the patient population increase with our modification, we believe we will be able to statistically prove its value. The long-term follow-up will be the subject of a future report. At the present time we feel the Payne Shunt with our modification may be the surgical procedure of choice for the morbidly obese patient.

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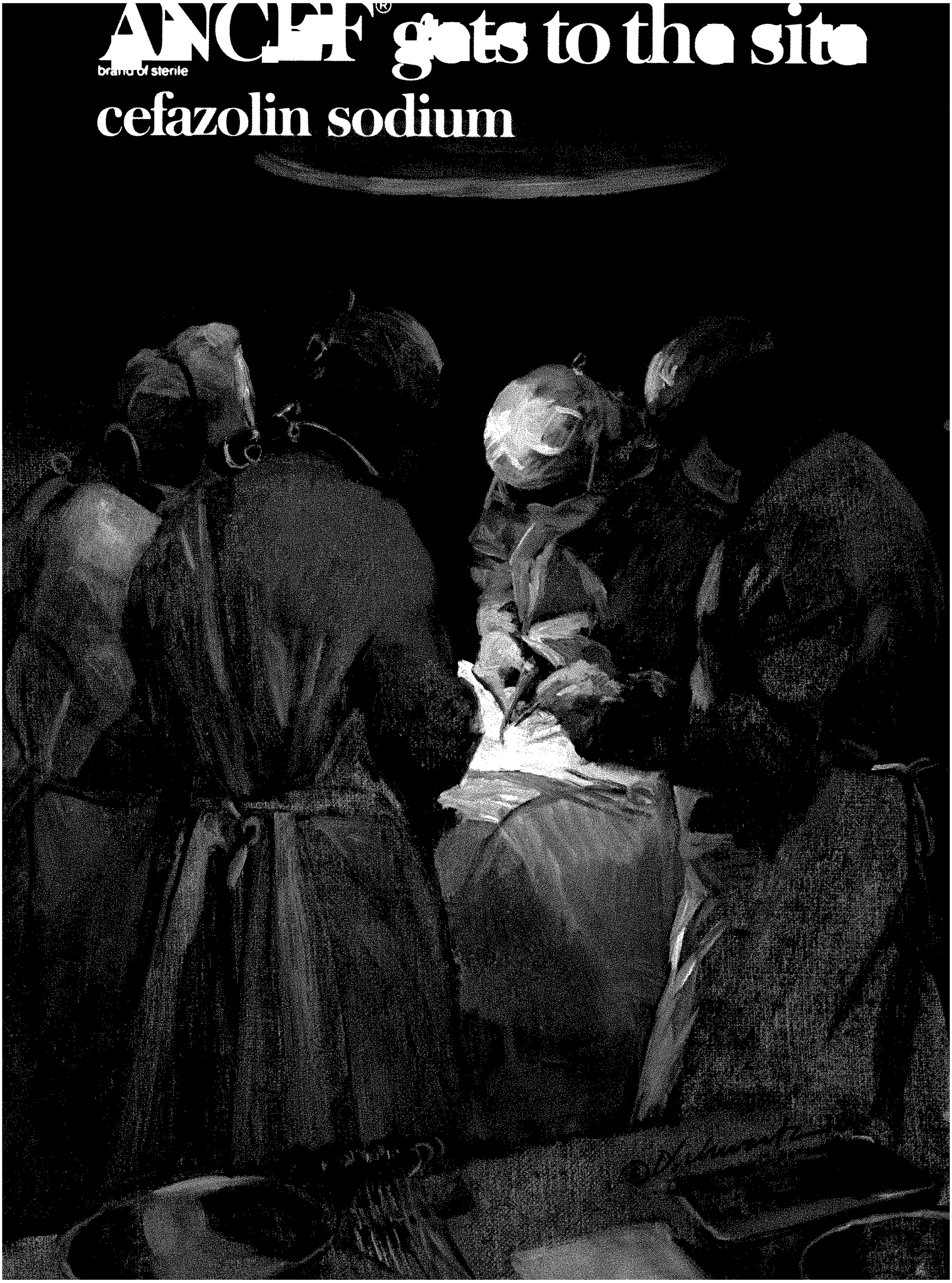
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Thrombotic Thrombocytopenic Purpura (TTP) and Splenectomy:

A Current Appraisal

IRA M. RUTKOW, M.D., M.P.H.*

From the Department of Surgery, The Johns Hopkins Hospital, Baltimore, Maryland

Thrombotic thrombocytopenic purpura (TTP) is a disease process characterized by microangiopathic anemia, fever, neurologic manifestations, renal abnormalities, and thrombocytopenia. These clinical findings are caused by vascular occlusions of the microcirculation. At present the utilization of splenectomy, in the treatment of this illness, remains a highly controversial subject. However, review of the literature reveals that 70% of the long term survivors of TTP had undergone splenectomy. This report presents five patients with TTP, four of whom had been splenectomized. Long term survival (greater than one year) was achieved in three individuals. It is recommended that splenectomy be considered as part of the initial management of all patients with TTP, in addition to high dose corticosteroids and antiplatelet drugs.

IT HAS BEEN OVER A HALF CENTURY since Moschcowitz first described "an acute pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries,"[9] which Singer later termed thrombotic thrombocytopenic purpura (TTP).[13] The clinical manifestations of this illness are due to vascular occlusions of the microcirculation causing a pentad of findings: microangiopathic anemia, fever, neurologic manifestations, renal abnormalities and thrombocytopenia. Although once considered a relatively rare problem there are now approximately 400 case reports, and TTP has assumed the status of a well recognized disease complex.

Removal of the spleen is considered one of the major therapeutic modalities available for the treatment of this illness. Although the first successful splenectomy for TTP was reported in 1951,[8] it was not until 1957 that a sustained remission, utilizing the dual therapeutic approach of high dose corticosteroids and splenic removal, was achieved.[11] During the subsequent two decades many additional forms of therapy have been utilized including; antimetabolites, antiplatelet drugs, heparin, streptokinase, exchange transfusions, and hemo- and peritoneal dialysis.

This report will present five patients diagnosed as having TTP. Four of these individuals underwent splenectomy, one died seven days following surgery, and three are alive and well, without recurrence after one to five years of follow-up. The one patient who had no operative intervention also expired.

Case Reports†

Case 1 (G.M. #498259). A 32-year-old white woman had complained of cardiac palpitations, fatigue and headaches for a two week period. She was admitted to the university hospital for work-up and diagnosis of anemia and thrombocytopenia. On physical examination she was noted to be moderately obese, with scattered ecchymotic areas on her trunk although the remainder of the examination was unremarkable. At that time the hemoglobin was 7.6 mg/100 ml with a hematocrit of 24%. The white blood cell (WBC) count was 4,600/mm^3, and the reticulocyte measurement was 15%. The admission platelet count was 15,000/mm^3. Peripheral blood smear demonstrated anisocytosis and schistocytes. Serum electrolytes were within normal limits as were the blood urea nitrogen (BUN), serum creatinine and serum bilirubin. Urinalysis revealed three red blood cells (RBC) and 6–10 WBCs per high powered field, and a 1+ proteinuria. Bone marrow aspiration showed hyperplasia with increased numbers of megakaryocytes.

A diagnosis of TTP was made and high dose corticosteroid treatment was begun. However, the platelet count continued to drop, and emergency splenectomy was performed. Postoperatively the platelet count began to rise immediately, and at time of discharge (14 days following admission) it was 640,000/mm^3.

The patient has remained asymptomatic, and without evidence of recurrence 5 years later. Pathological examination of the spleen was consistent with the diagnosis of TTP.

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* Robert Wood Johnson Clinical Scholar.

Submitted for publication: January 6, 1978.

† All patients were evaluated at the Boston University Medical Center, Boston, Massachusetts.

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Case 2 (V.S. #514791). A 56-year-old white woman was transferred from an affiliated hospital for evaluation of a comatose state present for 48 hours. Three weeks prior to transfer she had developed severe chest pain with dizziness and bilateral upper extremity numbness. Two weeks following this episode she was admitted to a local hospital because of confusion, dysarthria, facial asymmetry, generalized weakness and parethesia of the right upper extremity. The patient showed progressive aphasia culminating in the comatose state. Laboratory findings revealed a hematocrit of 22%, and a platelet count of 3000/mm^3.

On transfer to the university hospital both heart rate and blood pressure were within normal limits, but Cheyne-Stokes respirations were evident as well as ecchymotic areas over all extremities. She was febrile (100.2), with no response to painful stimuli. The liver and spleen were not palpable.

Laboratory findings were a hemoglobin of 6.1 mg/100 ml, and a hematocrit of 18%. White blood cell count was 10,900/mm^3, with a reticulocyte count of 9.2%. The platelets numbered 3,000/mm^3. Peripheral blood smear demonstrated schistocytes. Serum electrolytes were within normal limits although the BUN was 22 mg/100 ml and serum creatinine was 1.4 mg/100 ml. Total serum bilirubin was 4.0 mg/100 ml with a direct reacting fraction of 1.7 mg/100 ml. Urinalysis revealed numerous RBCs per high powered field, granular casts and 4+ proteinuria.

Preliminary diagnosis of TTP was made in addition to central nervous system lupus erythematosus. Treatment utilizing high dose corticosteroids and heparin was begun, but there was no improvement. Peritoneal dialysis was also instituted, again without benefit. The downhill course continued in spite of treatment, and she expired one week following admission. Consent for postmortem examination was not obtained.

Case 3 (B.T. #524168). A 35-year-old white woman, previously healthy, was referred from another hospital where she had presented 24 hours earlier with complaints of disorientations, fever and headache. On admission she was agitated and dysarthric. There was a moderate tachycardia with a fever of 101°. The patient was obese with multiple petechiae on the upper extremities. The liver and spleen were not palpable.

Laboratory examinations revealed a hemoglobin of 7.5 g/100 ml, and a hematocrit of 20%. The WBC count was 21,800/mm^3, with a platelet measurement of 2,000/mm^3. Peripheral blood smear showed poikilocytosis, schistocytes and tear drop forms. The serum electrolytes and BUN and serum creatinine were within normal limits. Total serum bilirubin was 2.7 mg/100 ml, with a direct reacting fraction of 1.2 mg/100 ml. There was a 2+ proteinuria on urinalysis.

A diagnosis of TTP was made, and treatment with aspirin suppositories, dipyridamole and methyprednisolone was begun. The morning following admission the neurological evaluation had worsened, and an emergency splenectomy was performed. Postoperatively she developed a retroperitoneal hematoma requiring 32 units of whole blood transfusion. Because of continued thrombocytopenia and a rapidly deteriorating neurological status it was decided to perform hemodialysis. The patient's clinical condition never improved with the highest platelet count being 30,000/mm^3. Seven days following admission she suffered a cardiac arrest and expired. Postmortem examination was denied by the family.

Pathological examination of the spleen showed the small trabecular arteries and arterioles to have a substantial subendothelial deposit of eosinophilic material which was PAS positive. This was felt to be consistent with the diagnosis of TTP.

Case 4 (S.C. #542863). A 40-year-old white man, in previous good health, was evaluated for hematuria and easy bruisability of two weeks duration. Physical examination revealed a well developed individual with numerous ecchymoses over his trunk and extremities. The liver was palpable 4 cm below the right subcostal margin, but the spleen was nonpalpable. Remainder of the physical examination, including the neurologic status, was within normal limits.

Laboratory data showed a hemoglobin of 10.3 mg/100 ml, and a hematocrit of 32%. The WBC count was 12,500/mm^3 with a reticulocyte measurement of 30%. Platelets were 27,000/mm^3. Peripheral blood smear demonstrated aniso- and poikilocytosis with occasional schistocytes. The serum electrolytes were within normal limits, but the BUN was 21 mg/100 ml, and the serum creatinine was 1.2 mg/100 ml. Urinalysis showed 5–10 RBCs per high powered field, numerous hyaline and granular casts and a 2+ proteinuria. Bone marrow aspiration revealed reactive hyperplasia with increased megakaryocytes.

The presumed diagnosis was TTP, and treatment was begun using high dose corticosteroids. Within 48 hours of admission the patient experienced a transient aphasia and right upper extremity weakness. Because of the deteriorating neurological status an emergency splenectomy was performed. Postoperatively he did well with resolution of the neurological deficits, and an increase in the number of platelets. On the fourteenth postoperative day he became febrile, and a diagnosis of left subphrenic abscess was made. This was drained although a small pancreatic fistula soon became evident. Total parenteral nutrition was started, and once the pancreatic drainage had substantially decreased an elemental diet was begun. The patient was discharged one month following admission with complete resolution of the TTP. Two year follow-up has shown the patient to remain in good health. Pathological examination of the spleen revealed severe congestion with occasional subendothelial deposits in the arterioles felt to be consistent with TTP.

Case 5 (W.P. #553440). A 26-year-old white man was treated at an affiliated hospital for fever, generalized urticarial rash and pharyngitis. Two days following this therapy he noticed the onset of darkened urine, and petechial eruptions on the extremities. One week later he was admitted to the same hospital after having been involved in an automobile accident in which he apparently had a loss of consciousness and question of seizure-like activity. He was placed on steroids, but within six hours of admission had a grand mal seizure, and was transferred to the university hospital with a presumptive diagnosis of TTP.

Physical examination revealed a now alert and fully responsive patient. Numerous petechiae were noted on the trunk and all extremities. The spleen was palpable 1 cm below the left subcostal margin, but the liver was nonpalpable. The remainder of the examination, including neurologic status, was within normal limits.

Laboratory data revealed a hemoglobin of 8.5 mg/100 ml, and a hematocrit of 25%. The WBC count was 12,600/mm^3 with a reticulocyte count of 14%. The platelet measurement was 17,000/mm^3. Peripheral blood smear showed polychromasia and schistocytes. Serum electrolytes, including BUN and serum creatinine, were within normal limits. There was gross hematuria and associated proteinuria in the urinalysis. Sternal marrow aspirate demonstrated a hypercellular marrow with marked megakaryocyte hyperplasia.

The patient was immediately begun on high dose corticosteroids and received platelet transfusions. On the second hospital day he had another seizure, and became unresponsive. An emergency splenectomy was performed, but the patient remained comatose. Twenty four hours following the removal of the spleen he underwent an exchange transfusion of 7 units of whole blood. By the third postoperative day he begun to show gradual improvement in comprehension and state of alertness. The platelet count rose to 320,000 mm^3, and the hematocrit increased to 36%. He was discharged 19 days following admission, and one year follow-up has shown no recurrence of the disease.

Pathological examination of the spleen showed small blood vessels with rare areas of subendothelial (PAS +) hyalinization. The histologic spectrum was felt to be consistent with the diagnosis of TTP.

Discussion

Although initially described in 1924,[9] and termed thrombotic thrombocytopenic purpura by Singer in 1947,[13] the number of reported cases was very small up to the early 1950's. Since that time there has been a sharp increase, and over 400 cases are presently known. A true increase in the incidence of the illness cannot be epidemiologically ruled out, but the accepted rationale is greater recognition and better reporting.

The etiology of this disease remains unknown even though its clinical presentation and subsequent course are now well documented. Among the varying etiologies which have been suggested are: allergic, autoimmune, infectious, toxic and vascular. It has also been stated that TTP is a syndrome, rather than a specific disease entity, because of the variety of presenting symptoms and signs, the overlap between this entity and the microangiopathic anemias, and the variable success of a wide range of therapeutic approaches, however, this remains to be proven. It appears to have a peak incidence in the third decade of life, with females being affected slightly more often than males.

As noted, in the five patients presented, the majority of individuals have very vague, nonspecific symptoms for a period of one to three weeks prior to development of the fulminant disease complex. The most frequently observed chief complaints were fatigue, headaches, and transient neurologic deficits.

The well known pentad of clinical findings are due to thrombotic vascular occlusions in the arterioles and capillaries of the brain, kidney, and throughout the microcirculation. These are caused by the deposition of a hyaline-like (PAS +) substance associated with local intimal proliferation, but without vasculitis. The occluding material is composed of fibrin and platelets, and this originally led investigators to believe that disseminated intravascular coagulation (DIC) was an integral part of the TTP phenomenon. It, however, has now been relegated to the role of a secondary reaction.

Approximately 50% of the patients will experience all five of the cardinal manifestations of TTP: microangiopathic anemia, fever, neurologic and renal abnormalities, and/or thrombocytopenia. However, both the anemia and the thrombocytopenic reaction are considered hallmarks of the illness, and those patients not having either of these manifestations must be considered to have a questionable diagnosis. The differential diagnosis of TTP includes: aplastic anemia, drug reaction, eclampsia, idiopathic autoimmune hemolytic anemia (IAIHA), idiopathic thrombocytopenic purpura (ITP), leukemia, paroxysmal nocturnal hemoglobinuria, periateritis nodosa, sepsis, systemic lupus erythematosus (SLE), and toxin exposure.

The laboratory findings are extremely important in establishing the final diagnosis. All bone marrow aspirates, in the cases presented, demonstrated marked hypercellularity with an increase in the number of megakaryocytes. The peripheral blood smears revealed aniso- and poikilocytosis with schistocytes. Renal manifestations ranged from minimal abnormalities to gross hematuria to 4+ proteinuria (Table 1).

Most striking of the laboratory findings were the extremely low admission platelet counts noted in the two patients (#2 and #3) who expired. It is likely that a more advanced stage of the disease was seen at the time of initial examination. The admission platelet count might prove to be of prognostic value with regards to the ultimate outcome of the therapy. Of the long-term survivors, both in this report and the literature, the vast majority have had admission platelet counts above 10,000/mm^3.[3]

Although the exact role of the spleen in TTP has not yet been demonstrated, the published reviews and the present series suggest splenomegaly to be present in approximately 20% of the individuals. Kardi has hypothesized that intrasplenic phagocytosis may be a major factor in the etiology of TTP, in that the platelets forming the vascular occlusions may have been damaged during their circulation through the splenic vasculature.[6] The different effects of splenectomy might be related to the varying times at which the procedure is performed, in relation to the course of the illness.

In a 1976 review of the TTP literature, over 340 cases were collected including at least 62 patients who had survived for three months or longer.[10] Since 1968 approximately 70% of the long-term survivors have received dual splenectomy and steroid therapy. A recent report concluded, ". . . because TTP in the majority of cases runs a fulminant course with death occurring rapidly it is imperative that therapy be instituted as soon as the clinical diagnosis has been made. It would seem that the use of steroids followed by splenectomy, as rapidly as possible, provides the best chance of a cure. . ."[12] This statement is tempered by the fact that there still remains a substantial number of individuals who succumb even though they have re-

TABLE 1. *The Clinical and Laboratory Manifestations of TTP*

	Case #1	Case #2	Case #3	Case #4	Case #5
Hemoglobin g/100 ml	7.6	6.4	7.5	9.9	8.5
Platelets/mm^3	15,000	3,000	2,000	27,000	17,000
Temperature (F°)	100	100^2	101	98^6	101
Urinalysis	3 RBCs 6–10 WBCs 1+ proteinuria	numerous RBCs granular casts 4+ proteinuria	2+ proteinuria	5–10 RBCs granular casts 2+ proteinuria	gross hematuria
Peripheral blood smear	anisocytosis schistocytes	schistocytes	poikilocytosis schistocytes	poikilocytosis anisocytosis schistocytes	polychromasia schistocyte
Neurological deficits	—	comatose confusion dysarthria weakness parathesia	agitation aphasia	aphasia weakness	grand-mal seizures comatose
Palpable spleen	no	no	no	no	yes
Therapeutic regimen	steroids splenectomy	steroids heparin dialysis	aspirin dipyridamole steroids dialysis splenectomy	steroids splenectomy	exchange transfusions steroids splenectomy
Outcome and follow-up	without recurrence (5 years)	expired	expired	without recurrence (2 years)	without recurrence (1 year)

ceived this combined therapeutic approach. In addition, it would be a natural consequence that the literature is positively biased in favor of the publication of successfully treated patients. Therefore, it would be presumptutous to draw any definitive conclusions concerning this mode of therapy. The recommended dosage schedule for the high dose corticosteroid preparations ranges from 100 to 2,000 mg of cortisone equivalents per day.[7] Specific protocols have included hydrocortisone (1,000–1,200 mg/day), prednisolone (320–1,000 mg/day) and prednisone (40–1,000 mg/day).[5]

In addition to splenectomy, steroids, and exchange transfusions[4] the other major therapeutic regimen, currently under investigation, is that of the antiplatelet drugs (*i.e.*, aspirin, Dextran 70 and dipyridamole). The most recent review of this form of therapy shows 18 long-term survivors, but in 11 of these splenectomy had been performed.[2] It should be noted that 6 of the 18 survivors were from reports in which the author stated quite specifically that any patient diagnosed with TTP should undergo splenectomy as part of the initial management of the illness.[5,7] Yet, the authors of the review suggest that removal of the spleen be performed only if the antiplatelet drug therapy is of no benefit. The recommended dosage schedule of the antiplatelet drugs is aspirin 600–1,200 mg/day, Dextran 500–1,000 ml/day, and dipyridamole 300–400 mg/day, all in equally divided doses.[2]

Clearly the data are not conclusive concerning any one specific type of therapy, but the fact remains that TTP runs a rapidly progressive and often fatal course. In view of the controversy surrounding the varied therapeutic modalities to treat TTP, and the published experience with this illness, it would seem most prudent for the initial management to consist of a combined approach. Once the diagnosis is made the patient should be immediately prepared for emergency splenectomy. Time is of the essence, and waiting for a deterioration in the neurologic status or a hoped for benefit of drug therapy may prove ultimately fatal to the patient. Concurrent with the preparation for emergency surgery treatment with high dose corticosteroids and antiplatelet drugs must be begun. The length of drug therapy will depend on the individual's clinical response.

Acknowledgments

I wish to thank L. Talarico, M.D. for providing the case histories George D. Zuidema, M.D. for his critical review of the manuscript and Beth Greenwald, B.A. for her research assistance.

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Temporary Loop Ileostomy in the Treatment of Crohn's Disease

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The use of a temporary loop ileostomy for fecal diversion in 15 patients with Crohn's disease is discussed. The indications for the use of ileostomy included both emergency and nonemergency situations. Emergency indications included cases of acute peritonitis secondary to perforated bowel or abscesses, and intestinal obstruction. In nonemergency settings ileostomy was used either in conjunction with other surgery that was thought to have a significant risk of anastomotic leakage or to prepare a patient for major resectional surgery. It was the impression of the author's that temporary loop ileostomy was a helpful adjunct in the management of certain difficult cases of Crohn's ileocolitis.

PROXIMAL DIVERSION of the fecal stream by transverse colostomy is a well established procedure in the treatment of a variety of left sided colonic lesions such as carcinoma and diverticulitis. Less well established is the place of ileostomy as a temporary diversion for disease of the distal small bowel and proximal colon, particularly in Crohn's disease.

When surgery is indicated in Crohn's disease, resection of the diseased bowel is usually the most satisfactory treatment. Ileostomy has been rarely used on an elective basis, unless combined with a total proctocolectomy. There have been several reports however, on the use of ileostomy in certain difficult problems associated with Crohn's disease. Goligher[3] has recommended the use of an ileostomy in the treatment of fecal fistulas in this disease. In 1971[2] two of the present authors reported on the use of ileostomy for complicated cases of ileocolitis. Both loop and end ileostomies were used in this series. More recently Alexander-Williams[1] also reported on the use of loop ileostomy for fecal diversion in granulomatous disease. Because of our increasing reliance on loop ileostomy in certain cases of Crohn's disease we have reviewed our personal experience with this procedure over the past three years. The results as well as the indications for the use of loop ileostomy in both emergency and nonemergency settings forms the basis of this report.

Clinical Material and Indications

During the past three years the authors have used a loop ileostomy as part of the surgical treatment in 15 patients with Crohn's ileocolitis. The anatomic distribution of the granulomatous disease was: seven ileocolites, six ileitis, and two colitis. Eight patients had at least one prior surgical procedure for their disease. All ileostomies were constructed in a manner similar to that described by Turnbull.[6]

The indications for surgery have been divided into emergency and nonemergency situations, and are shown in Table 1. Of the nine patients who required emergency surgery, five were for perforated mesenteric abscesses, two were for anastamotic leaks in the early postoperative period, one was for a free perforation and one was for acute intestinal obstruction. All of the patients in this group, except the one with intestinal obstruction, had obvious peritonitis with gross contamination of the peritoneal cavity.

In nonemergency situations five of six patients had their ileostomies performed in conjunction with other elective procedures that were thought to have a significant risk of anastamotic leakage. Three of these patients had ileoproctostomies, one had two simultaneous resections (ileocolic and sigmoid), and one had an ileocolic resection in the presence of a grossly contaminated field. The final patient had a loop ileostomy performed as the sole procedure because she was in a debilitated state and it was felt that she could not tolerate an extensive resection. Several representative case histories are summarized in Table 2. Figures 1 and 2 refer to Case 2 and 4 in Table 2.

• Presented at the New York Surgical Society, December 14, 1977.

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Submitted for publication: December 27, 1978.

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TABLE 1. *Indications for Surgery*

Emergency	Nonemergency
Abscess (± perforation)—5	Conjunction with other surgery
Anastomotic breakdown—2	ileoproctostomies—3
Free perforation—1	multiple resections—1
Acute intestinal obstruction—1	resections with contamination (pus, multiple fecal fistulae, *etc.*)—1
	Sole procedure
	malnourished patient with complicated disease—1
	severe perianal disease—0

Results

The outcome of the 15 patients who were treated with loop ileostomy are summarized in Table 3. Nine patients had their temporary ileostomies closed without complications. Two patients still have their ileostomies and are awaiting resectional surgery and closure. Two patients had their loop ileostomies converted to permanent end ileostomies.

There were two deaths in the series. The first patient was a 70-year-old female with Crohn's colitis who presented with sepsis and generalized peritonitis as well as bilateral pulmonary emboli. She was found to have multiple intramesenteric abscesses as a result of a localized perforation of her sigmoid colon. Drainage and a loop ileostomy was the only procedure undertaken because of the severity of systemic illness. She died postoperatively of pulmonary insufficiency. The second patient (Fig. 3) was a 68-year-old woman who had undergone two previous bowel resections, and presented with an ileocutaneous fistula and recurrent disease at the site of a previous ileosigmoidostomy. She underwent a sigmoid resection as well as an ileocolic resection of the formerly bypassed segment of ileum, and had an ileoascending colostomy performed. Postoperatively she developed a leak at

TABLE 2. *Case Reports*

	Age & Sex	Duration Symptoms	Diseased Segment	Indications For Surgery	Procedure	Follow-up
1. CP	40, F	23 y	Recurrent disease at previous ileocolic anastomosis	Perforated Mesenteric Abscess	Drainage and Loop Ileostomy	4 months later a secondary ileocolic resection was done, and following that the ileostomy was closed.
2. ER (Fig. 1)	32, M	20 y	Colon, distal small bowel and duodenal-colic fistula	Free perforation of the terminal ileum	Exteriorization of the perforated ileum, drainage and proximal loop ileostomy	Doing well 9 months after surgery.
3. GQ	31, M	1 y	Terminal ileum and possible sigmoid colon	Acute intestinal obstruction	Loop ileostomy	Ileocolic resection performed 2 months later after sigmoid was found to be normal. 1 month later ileostomy was closed.
4. LL (Fig. 2)	18, F	5 mo	Terminal ileum and sigmoid colon with ileosigmoid fistula and ileocutaneous fistula	Elective removal of diseased bowel and fistula	Ileocolic and sigmoid resection with loop ileostomy	2 months later loop ileostomy was closed.
5. AB	69, M	27 y	Colon (with rectal sparing) sigmoid stricture and colocutaneous fistula	Elective resection of diseased colon	Ileoproctostomy with proximal loop ileostomy	2 months later the ileostomy was closed.
6. MS	50, F	10 y	Recurrent disease of the rectum at a previous ileoproctostomy	Severe rectal disease with malnutrition and weight loss	Loop ileostomy	4 months later an abdominal perineal resection and permanent ileostomy were performed

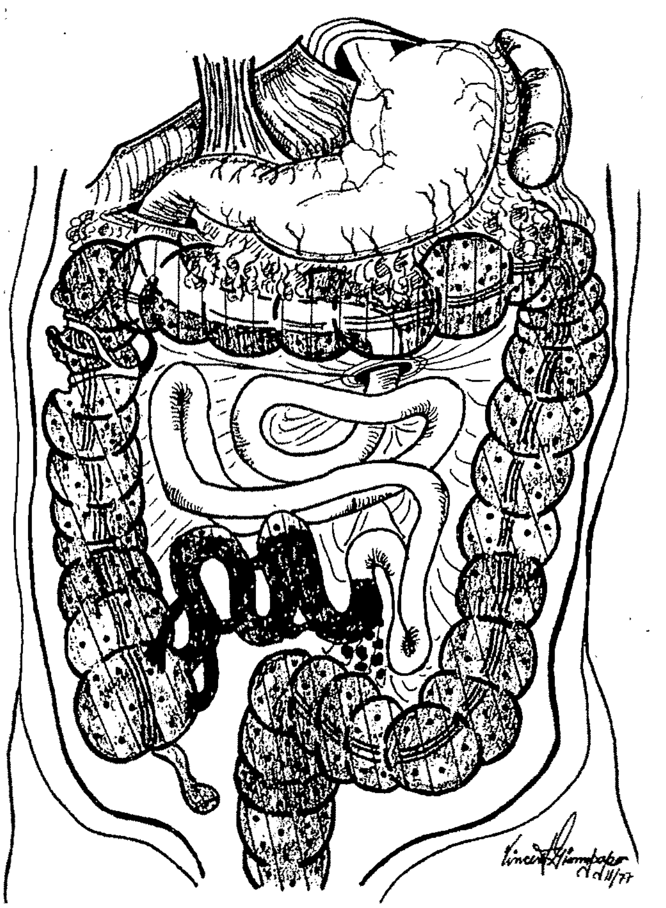

FIG. 1. E.R., Free perforation of the terminal ileum in a patient with extensive disease of the colon, terminal ileum and a duodenal-colic fistula.

the colocolonic anastamosis. Loop ileostomy and drainage was performed but she subsequently died of continued sepsis.

Discussion

We have found a temporary loop ileostomy to be of particular value in emergency surgery for Crohn's disease. Although free perforations of the intestine are rare in this disease,[4,5] their treatment is difficult. Aside from technical problems, the patients are frequently quite ill and often on high doses of steroids. Goligher[3] recommended resection of the diseased bowel with an end ileostomy and mucous fistula. Menguy[5] has proposed resection and a double-barrel cutaneous ileocolostomy. We agree that resection of a freely perforated segment of diseased bowel is the optimum treatment. If the peritoneal cavity is badly contaminated, or if the patient is a particularly poor surgical risk, an anastomosis should not be done. In more favorable circumstances in which an anastamosis is performed, the addition of a proximal diverting ileostomy may be a valuable measure. If the granulomatous disease is quite extensive and the patient appears unable to tolerate a major resection, exteriorization of the perforated segment with proximal loop ileostomy is another alternative.

Perforation of diseased bowel at the mesenteric border with the formation of a mesenteric abscess is a much more common occurrence in Crohn's disease. These patients may present with an acute perforation of this type of abscess. We have successfully treated patients in this category with drainage and ileostomy without resection. The resection of the diseased bowel is then done at the later date under elective conditions when the patient is in better condition.

Acute intestinal obstruction due to ileitis can usually be relieved with a Kanter tube. If surgery is indicated, resection of the diseased segment is the usual treatment. If there is a great disparity in the size of the proximal and distal bowel, or if the extent of the disease is not clear, a loop ileostomy may be

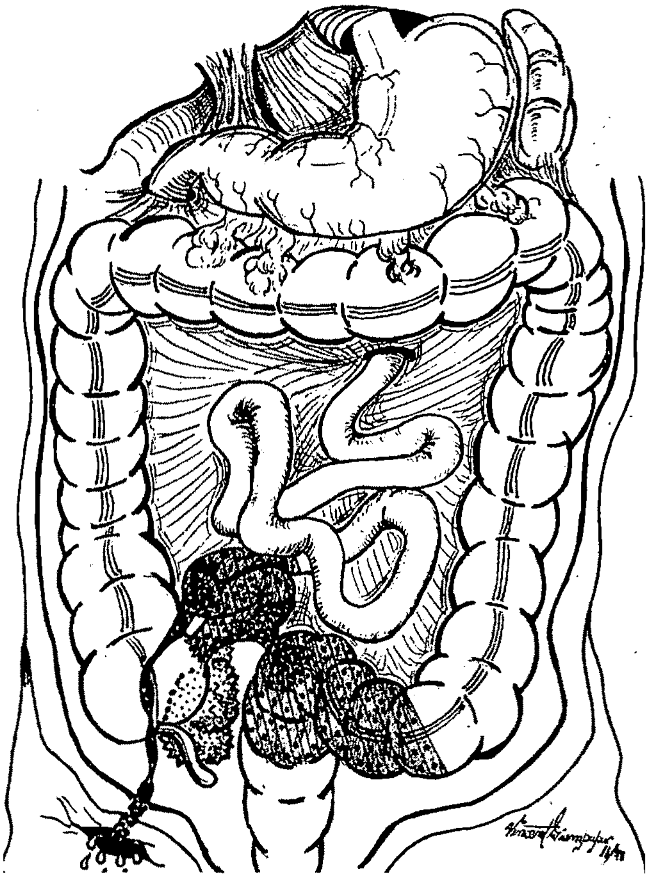

FIG. 2. L.L., Granulomatous disease of the terminal ileum, sigmoid colon, with an ileocutaneous and an ileosigmoid fistula.

TABLE 3. *Result of Treatment with Temporary Loop Ileostomy (15 Patients)*

Result	Number
Ileostomy Closed	9
Await Resection and Closure	2
Resection and Conversion to a Permanent Ileostomy	2
Died	2

performed as a temporary measure, instead of a resection and anastamosis.

In nonemergency settings, loop ileostomy has been found to be useful in two settings. The first use is in complicated surgical procedures in which the risk of anastamotic leakage is high. In these cases the ileostomy is used for temporary diversion, along with a definitive resection. Examples of this use are in multiple simultaneous resection (ileocolic plus sigmoid, *etc.*), difficult subtotal colectomies with ileoproctostomy, resections performed in the presence of gross infection, or the presence of multiple external fecal fistulas.

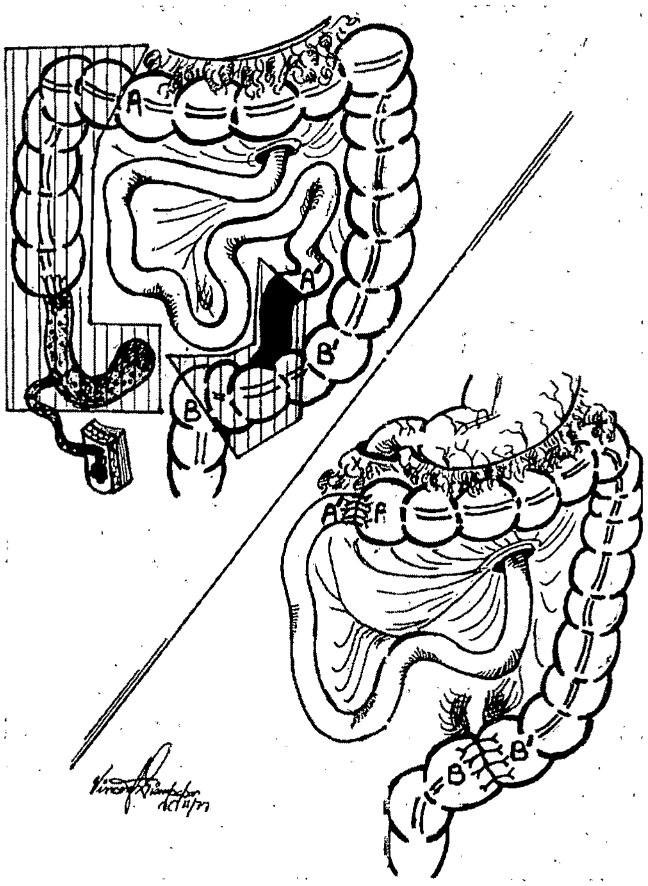

FIG. 3. This 68-year-old woman, had two previous bowel resections and recurrent disease at an ileosigmoidostomy (A). She underwent an ileocolic resection and a reanastomosis of the sigmoid colon.

In the second group ileostomy is performed as the sole initial procedure. Examples of this are patients with severe fulminating disease who were in a poor nutritional state who could not tolerate extensive resectional surgery (and did not improve with hyperalimentation). Patients with extensive perianal disease may also occasionally fall into this category.

In summary, we feel that temporary loop ileostomy has a place in the management of Crohn's disease. It can be used in both emergency and nonemergency settings as the sole form of therapy or in conjunction with other surgery. It is of particular value when either the patient is extremely sick or debilitated or when the surgery necessary to treat the disease is difficult. The construction of a loop ileostomy has been found to be a simple procedure which is essentially completely diverting and can easily be closed or resected at a later date. We stress the fact that in almost all cases the ileostomy is a temporary measure and is not considered definitive therapy. We feel that the use of this procedure in properly selected patients will aid in improving both mortality and morbidity.

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(continued from page 81A)

New Concepts in Maxillofacial Bone Surgery. Bernd Spiessl (ed.). 194 pp. New York, Springer-Verlag. 1976. $64.00.

THIS EXTREMELY WELL ORGANIZED and beautifully printed book is concerned with the most recent advances in maxillofacial surgery of the Swiss group at the University of Basle. The primary emphasis of their work is related to the results of experimental studies concerning the association for the study of internal fixation (ASIF) and their techniques in facial bone reconstruction. The engineering principles involved with this type of reconstruction as applied to facial bones are clearly demonstrated by experimental studies and confirmed by clinical experiences. The success of absolute bony fixation and the use of the dynamic compression plate and dynamic compression implant for extensive reconstruction of the maxilla and mandible is clearly defined.

Of special importance to maxillofacial surgeons are the results of their careful analysis of the best techniques of bone grafting as enhanced by the utilization of the ASIF principles. These principles are further projected into illustrative cases involving severe fractures, extensive traumatic injuries, and postcarcinoma resections, all of which require reconstruction of facial bones.

Especially unique in this extremely worthwhile book is the careful documentation of results of all of their experimental and clinical studies. This allows the reader to adequately review the judgments of the authors.

The failure to define the need for prophylactic antibiotic coverage during extensive maxillofacial reconstruction despite an extremely well controlled attempt adds appropriate data to the experiences of surgeons operating in other regions who have similar attitudes.

The bibliography is excellent. Sources of special instruments needed for the concepts presented are also included.

This book is a compendium of the laboratory and clinical experiences of a highly skilled and very experienced team of Swiss maxillofacial surgeons who have "set the standard" by this work.

JEROME E. ADAMSON, M.D.

Blood Transfusion for Clinicians. John Wallace. 351 pp. New York, Churchill Livingstone. 1977. $22.50.

THE FIELD OF blood transfusion therapy has changed dramatically over the past 15 years. What was once a largely administrative matter of giving whole blood if laboratory compatibility testing seemed to demonstrate compatibility, has changed to an active medical specialty. The changes have been rapid, but subtle, and many people in other specialty fields are not aware of these changes. Dr. Wallace, in his excellent book, has been one of the first to outline in considerable detail the types of changes and their clinical significance. The description and treatment of the blood components that are now available is extensive and quite useful.

The clinical importance of the different blood groups, and hemolytic disease of the newborn are treated well, and are up to date. The tissue typing-HLA section is short, but it is written nicely, and permits a person not actively in the field to come abreast of recent developments. The hazards of blood transfusion and its future are well covered.

This short, easily readable book represents a first in the literature on blood transfusion therapy, and should be very helpful to people in other specialties that would quickly like to come abreast of the field.

Relatively few references are cited in the different chapters but the book equally is not intended as an exhaustive review of the literature.

The slant of the book (not unreasonably) is presented with the general point of view of blood transfusion therapy in the United Kingdom. Many of the expiration dates and permissible storage temperatures for different blood components are at variance with those permitted in the United States. Additionally there is considerable discussion of pooled, and freeze-dried plasma. Use of these was abandoned in the United States years ago. These matters are details that do not really detract from the general usefulness of this excellent book.

CHARLES E. HUGGINS, M.D.

Diagnostic Bronchoscopy (Third edition). Peter Stradling. 148 pp. New York, Churchill Livingstone. 1977. $35.00.

THIS IS A BEAUTIFULLY DONE monograph. It accomplishes very well its goals—to review and educate the student who is learning bronchoscopy and to offer the bronchoscopist an atlas for familiarizing himself with the pathology he will be encountering. The author clearly emphasizes that bronchoscopy is learned by experience and the monograph is to serve as an introduction to a normal and pathologic anatomy. Particularly good are the chapters on "Indications for Bronchoscopy" and "Bronchofibreoscopy." The author's vast experience is clearly evident by the number of color plates used to illustrate the normal and pathologic anatomy of the tracheobronchial tree. These are beautifully reproduced and literally every conceivable condition one might encounter is represented.

This excellent monograph would be a valuable addition to the library of any physicians who do bronchoscopy as well as residents in surgical and pulmonary medicine training programs.

WALTER G. WOLFE, M.D.

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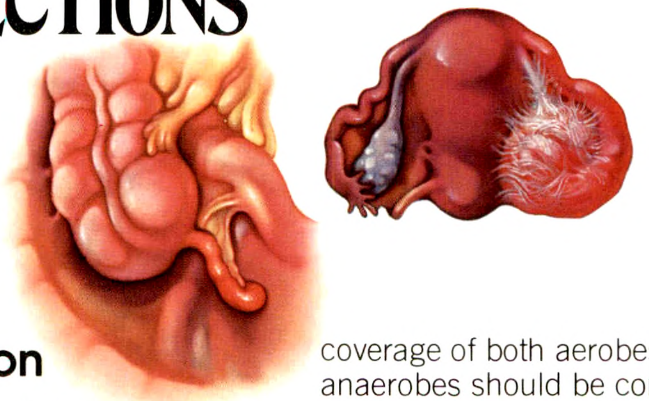
THE BIPHASIC NATURE OF SERIOUS INTRA-ABDOMINAL/PELVIC INFECTIONS



Introduction

The biphasic clinical nature of serious intra-abdominal and female pelvic infections may be related to sequential dominance first of aerobes and then of anaerobes. Antimicrobial coverage of both aerobes and anaerobes should be considered during all stages of serious intra-abdominal and female pelvic infections.

The majority of these infections are polymicrobial. During the early, toxic phase, aerobes are

Acute Phase:
Peritoneal Response

Peritoneal contamination with polymicrobial (aerobic and anaerobic) flora from the bowel or vagina may occur during surgery or as a result of trauma, septic abortion, or perforating diseases such as appendicitis.

Clinical signs in the acute phase include increasing abdominal tenderness and fever. Bacteremia, which may progress to septic shock, occurs fairly frequently. In female pelvic infections, bacteremia and septic pelvic thrombophlebitis are always a threat because of the rich vasculature of the female pelvis.

Initially, antimicrobial therapy directed against aerobes such as *Escherichia coli* often results in defervescence and clinical improvement. Failure of the patient to respond or recurrence of symptoms may indicate anaerobic involvement. *B. fragilis* is the anaerobe most frequently isolated in patients with intra-abdominal sepsis or serious female pelvic infections.

Late Phase:
Peritoneal Response

The clinical course may progress to walling off of the infection and subsequent abscess formation. These collections of pus can be located intraperitoneally, retroperitoneally, or within the viscera.

Progression from peritonitis to abscess formation may be an insidious process or may be marked by sudden deterioration of the patient who had been recovering. At this point, failure to respond to appropriate antibiotic therapy should alert the clinician to the possibility of intra-abdominal or pelvic abscess formation and

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generally the dominant pathogens; the coexistent anaerobes may contribute to the clinical picture. In the patient who progresses to the late phase and develops an abscess, anaerobes (especially *Bacteroides fragilis*) are the dominant isolates.

---

the potential need for operative intervention.

In both the early peritonitis stage and the later abscess stage, culture of purulent material yields aerobes and anaerobes in the majority of instances. In fact, anaerobes have been isolated from 90% to 96% of intra-abdominal infections associated with bowel perforation. Anaerobes such as *B. fragilis* have been isolated in 80% to 100% of patients with pelvic abscesses studied with appropriate techniques of specimen collection and culture.

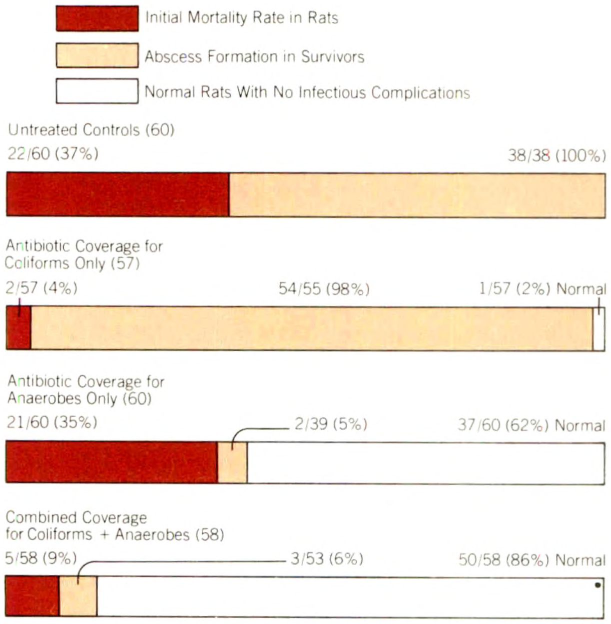
For information about one antibiotic to consider in treating serious infections due to anaerobic pathogens, please turn the page.

Upjohn

INDUCED PERITONEAL SOILAGE

The sequence of events that follow experimental induction of peritoneal soilage in rats parallels the biphasic course of this disease. Although animal data cannot be directly applied to humans, this model helps explain the pathogenesis.

A standardized inoculum of rat colonic contents containing both aerobic and anaerobic organisms was implanted into the peritoneal cavity of male Wistar rats. The animals were observed for response and survivors were sacrificed after ten days. The rats developed a two-stage disease: initial, acute peritonitis and later, intra-abdominal abscesses. Mortality and progression of these stages varied sharply with antimicrobial coverage for aerobes, anaerobes, or both.



In this study, coliform organisms appeared to be responsible for the early mortality associated with fecal peritonitis, whereas *B. fragilis* and other anaerobes were associated with later abscess formation.

Upjohn

THERAPEUTIC CONSIDERATIONS...

Anaerobic activity

Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal and female pelvic infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection; serious lower respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; and serious skin and soft-tissue infections caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, in vitro dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Indications include: serious lower respiratory tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances, the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible in vitro and were successfully eradicated from the clinical lesions.

Other therapeutic considerations

1. Cleocin PO_4 (clindamycin phosphate injection) is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section of the brief summary on the following page.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

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*Clostridia are more resistant than most anaerobes to clindamycin. Some species, eg, *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

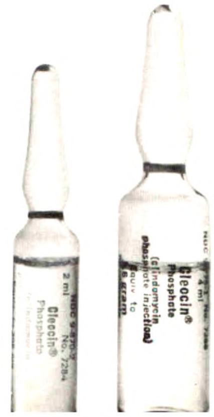
Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative. MED B-5-S J-6219-9

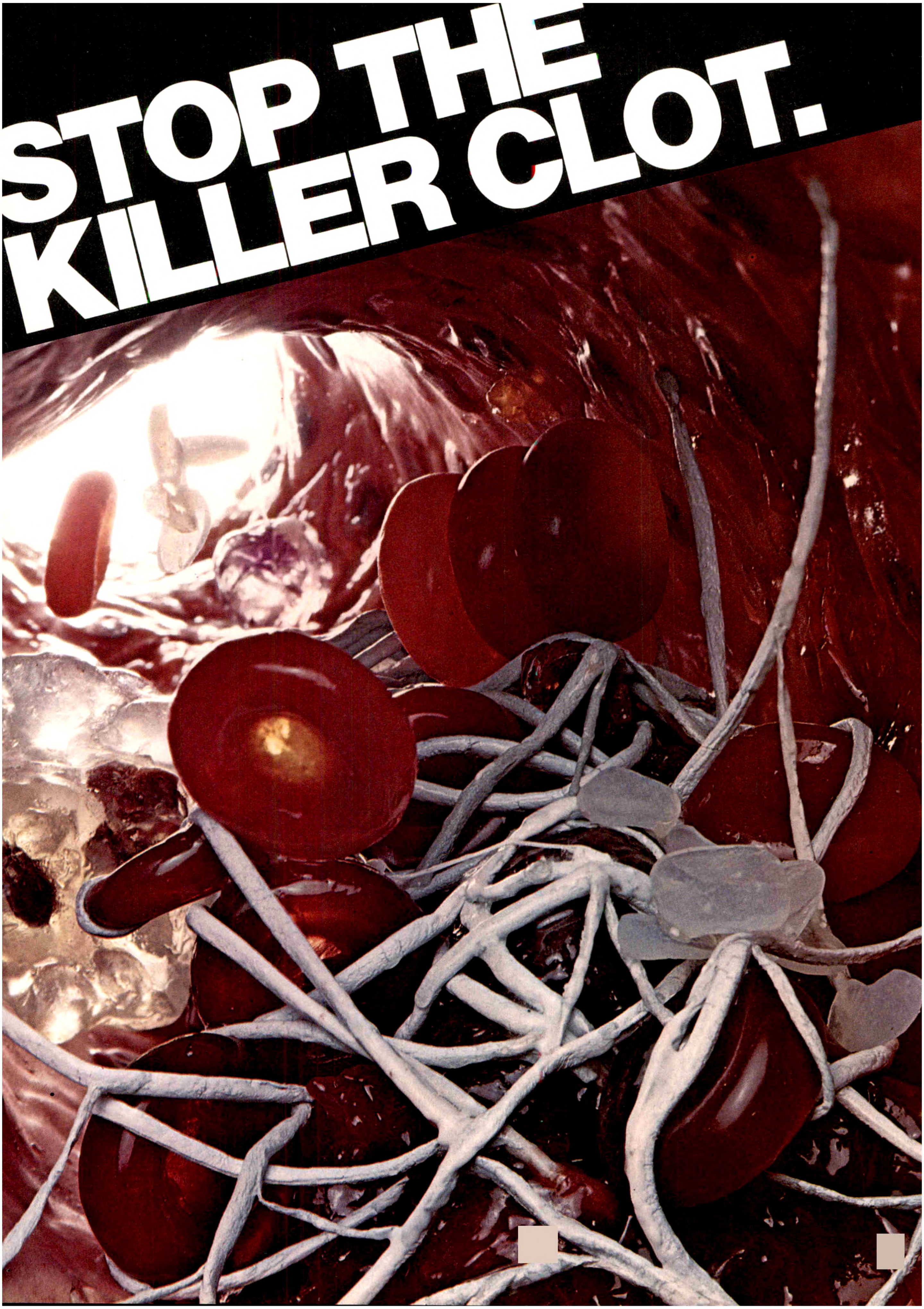


STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001


STOP THE
KILLER CLOT.

Announcing thrombus prevention without anticoagulation.

NEW

After extensive trials, RHEOMACRODEX® (dextran 40) is now the only dextran indicated for the prevention of postoperative venous thrombosis and pulmonary embolism in the high-risk patient.

NEEDED

Deep venous thrombosis and pulmonary embolism are among the most serious complications of surgery and trauma. Postoperative thromboembolic disease may strike up to 54% of surgical patients, especially those undergoing hip surgery.[1] Pulmonary embolism alone may account for 200,000 deaths in the United States annually.[2,3]

PROVED

Dramatically reduces the incidence of postoperative thromboembolic disease.

High-Risk Operative Category	Percent of Patients Developing Postoperative Thromboembolic Disease	
	Control Group	Rheomacrodex Group
Hip Arthroplasty[4]	39%	12%
Orthopedic Surgery[5]	20%*	0%*
General Surgery[6]	10%	4%
Gynecologic Surgery[7]	7%†	1%†

*Diagnosed as definite disease. An additional 11% of controls and 5% of Rheomacrodex patients were diagnosed as having possible thromboembolic disease.

†Figures pertain only to patients with pulmonary emboli.

SAFE, CONVENIENT USE

Used as directed, RHEOMACRODEX has an impressive record of patient safety, and does not usually provoke excessive bleeding, as may anticoagulants. As with all drugs, the physician should familiarize himself with all the information required to use the drug safely (see prescribing information).

DOSAGE

- Choose according to risk of thromboembolic complications
- Initiate during surgery
- ℞ Day of operation: 500 to 1,000 ml
  Postop. days 1-3: 500 ml/day
  Postop. days 4-14: 500 ml every 2 or 3 days

IN YOUR NEXT HIGH-RISK PATIENT, RHEOMACRODEX CAN

- Smooth your patient's surgical and postoperative course
- Reduce the incidence of deep venous thrombosis and pulmonary embolism
- Reduce platelet adhesiveness
- Eliminate anticoagulation

Pharmacia

Rheomacrodex®

(dextran 40)

THE RISK REDUCER.

◀ An artist's conception of a venous thrombus principally composed of fibrin, platelets (visible at center right) and erythrocytes. A leukocyte appears at center left. Proportions are not to scale.

See following page for prescribing information.

Rheomacrodex® (dextran 40)

Indications

Rheomacrodex is indicated for use in prophylaxis therapy against venous thrombosis and pulmonary embolism in patients undergoing procedures known to be associated with a high incidence of thromboembolic complications, such as hip surgery.

Contraindications

Known hypersensitivity to dextran. Marked hemostatic defects of all types (thrombocytopenia, hypofibrinogenemia, etc.), including those caused by drugs (heparin, warfarin, etc.). Marked cardiac decompensation. Renal disease with severe oliguria or anuria.

Warnings

Although infrequent, severe and fatal anaphylactoid reactions, consisting of marked hypotension, and/or cardiac and respiratory arrest have been reported. Therefore, it is strongly recommended that patients be observed closely during the early part of the infusion period.

As Rheomacrodex (dextran 40) is a colloid hypertonic solution, it will attract water from the extravascular space. This fluid shift should be considered when the drug is administered intravenously to poorly hydrated patients.

Renal excretion of dextran produces an elevation in urine viscosity and specific gravity proportional to the urine dextran concentration. If signs of dehydration are noted, additional fluids should be administered.

Renal failure, sometimes irreversible, has been reported to occur following the use of Rheomacrodex. While the preexisting clinical condition of these patients could account for their oliguria and/or anuria it is possible that the administration of Rheomacrodex may have contributed to their development.

Occasional abnormal renal and hepatic function values have been reported following intravenous administration of Rheomacrodex.

Caution should be employed when Rheomacrodex is administered to patients with active hemorrhage as the resulting increase in perfusion pressure and improved microcirculatory flow may result in additional blood loss.

Administering infusions of Rheomacrodex that exceed the recommended dose should be avoided, since a dose-related increase in the incidence of wound hematoma, wound seroma, wound bleeding, distant bleeding (hematuria and melena), and pulmonary edema has been observed. Recommended doses should never be exceeded in patients with advanced renal disease, since excessive doses may precipitate renal failure.

Usage in Pregnancy: Safe use of Rheomacrodex has not been established with respect to adverse effect on fetal development. Therefore, it should not be used in early pregnancy or in women of childbearing age unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions

In individuals with normal hemostasis, dosages of Rheomacrodex up to 15 ml/kg body weight produce variable, usually small changes in coagulation. At these dosages, slight decreases in platelet adhesiveness occur, and decreases in fibrinogen, factor V and factor IX are usually only slightly greater than might be expected from hemodilution alone. Although dosages in this range markedly decrease factor VIII, they generally do not prolong bleeding time significantly. Since changes in coagulation and hemostasis tend to be more pronounced following trauma or major surgery, all patients should be observed for early signs of bleeding complications. Some of the changes induced by dextran may be reversed by infusion of factor VIII concentrate.

Care should be taken to prevent a depression of the hematocrit below 30 vol. %.

In patients who have received Rheomacrodex, blood sugar determinations that employ high concentrations of acid may result in hydrolysis of dextran, yielding falsely elevated glucose assay results. Blood typing and cross matching procedures employing enzyme techniques may give unreliable readings if the samples are taken after infusion of Rheomacrodex. Other blood typing and cross matching procedures are not affected.

It is recommended, therefore, that, whenever possible, blood samples for the above determinations be drawn prior to initiating infusion of Rheomacrodex.

Adverse Reactions

Since Rheomacrodex (dextran 40) has a very low degree of branching, it is relatively free of antigenic effect. Hypersensitivity reactions have, however, been reported with Rheomacrodex. These can range from mild cutaneous eruptions to generalized urticaria, nausea, vomiting, headache, fever, tightness of the chest, wheezing and, rarely, to anaphylactoid (allergic) shock. Since such reactions usually develop in the first few minutes following initiation of therapy, patients should be observed during the initial infusion. If any of the above adverse symptoms appear, the infusion should be stopped immediately.

Dosage and Administration

Prophylactic Therapy of Venous Thrombosis and Thromboembolism

The dosage of Rheomacrodex should be chosen according to the risk of thromboembolic complications, e.g., type of surgery and duration of immobilization. In general, treatment with Rheomacrodex should be initiated during surgery. 500 to 1000 ml (approximately 10 ml/kg body weight) should be administered on the day of the operation. Treatment should be continued at a dose of 500 ml daily for an additional two to three days. Thereafter, and according to the risk of complications, 500 ml Rheomacrodex may be administered every second or third day during the period of risk, for up to two weeks.

How Supplied

Rheomacrodex (dextran 40) is available as a sterile, nonpyrogenic solution in 500 ml infusion bottles, six bottles per case, and is available as:

Rheomacrodex 10% w/v in normal saline NDC No. 0016-0211-65
Rheomacrodex 10% w/v in Dextrose 5% in Water NDC No. 0016-0212-65

Rheomacrodex has a tendency to crystalize when subjected to temperature variations or when stored for long periods at elevated temperatures. Storage should therefore be at a constant temperature, preferably not exceeding 25°C (77°F). If flakes of dextran are present, heat at 100°-110°C until complete dissolution is achieved.

Keep from cold during transport.

Caution: Federal law prohibits dispensing without prescription.

For complete details including dosage please see full prescribing information.

References

1. Evarts CM: *Critical Care Medicine 4*:62-66, March-April 1976. 2. Brown DW, Wells HP, Ripple RC: *Today's Clinician 2*:14-19, January 1978. 3. Salzman EW, Harris WH: *J Bone and Joint Surgery 58-A*:903-913, October 1976. 4. Salzman EW, Harris WH, DeSanctis RW: *New Engl J Med 284*:1287-1292, June 10, 1971. 5. Langsjoen PH, Murray RA: *JAMA 218*:855-860, November 8, 1971. 6. Jansen H: *Acta Chir Scand Suppl* 427, 1972. 7. King CR, Daly JW: *Amer J Obstet Gynec 123*:46-49, September 1, 1975.

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APPLIED SURGICAL PATHOLOGY

Edited by
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The role of biopsy and frozen section in diagnosis has been emphasized.

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McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., 174:58, 1971.

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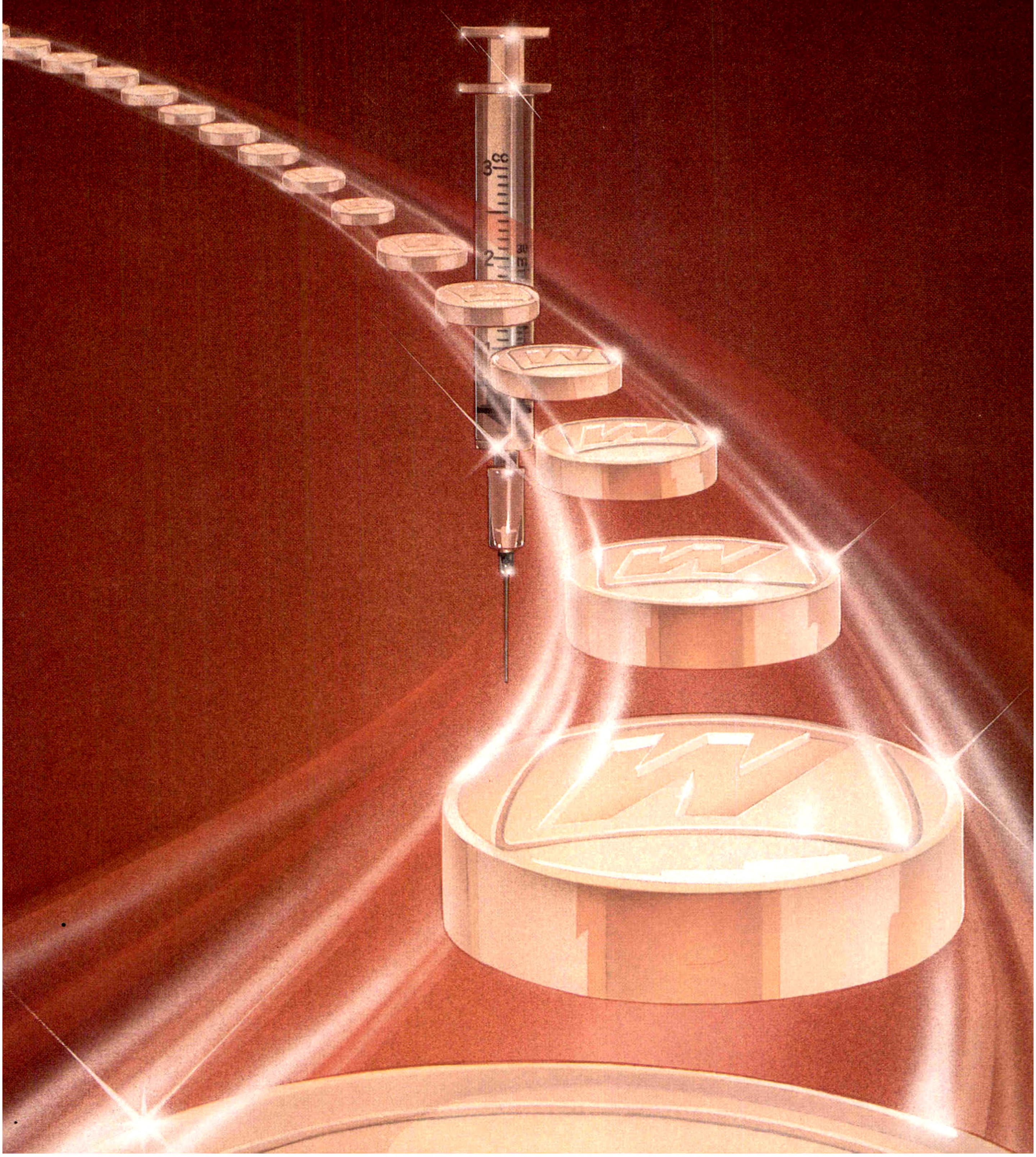


Potent - Dependable - Nonopiate

Talwin® HCl 50 mg.

brand of · equivalent to 50 mg. base
pentazocine HCl tablets, NF

Relieves pain as well as 60 mg. of codeine.

MILD ANALGESICS OFTEN DON'T WORK:

In a double-blind single dose study involving 225 adult inpatients, the comparative efficacy of 650 mg. aspirin, 65 mg. dextropropoxyphene, and 50 mg. pentazocine for relief of postoperative pain was recorded.[1]

- All patients were suffering from moderate or severe pain.
- Pregnant women as well as patients with known renal, respiratory, cardiac, or hepatic insufficiency were excluded.
- The onset of action of pentazocine was rapid.
- Although aspirin, dextropropoxyphene, and pentazocine produced significant relief from pain, pentazocine was significantly more effective at a half hour.
- Side effects were recorded for 16 patients: in the aspirin group 2 patients complained of drowsiness and 1 of dizziness. In the dextropropoxyphene group 5 patients vomited and 3 patients complained of drowsiness or dizziness, while 5 patients who had received pentazocine complained of dizziness.
- Pentazocine should be an oral analgesic of choice for treatment of postoperative pain.

Opiates are too addictive, too restrictive:

"Despite their potent analgesic action, the morphine-like analgesics have disadvantages that limit their usefulness: respiratory depression, nausea, vomiting, constipation, cardiovascular effects (hypotension, bradycardia), histamine release, and in some patients, an increase in intracranial pressure. Other adverse reactions include miosis, spasm of the biliary and urinary tracts, and rarely, hypersensitivity phenomena (urticaria, rash, and anaphylactic reactions). Frequent repeated use produces psychic and physical dependence."[2]

Oral Talwin shows infrequent occurrence of certain adverse effects as:

- Severe respiratory depression
- Hypotension
- Constipation
- Urinary retention
- Tachycardia

Among RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions—hallucinations (usually visual)—have cleared spontaneously within a period of hours. Withdrawal symptoms after prolonged use of Talwin for the relief of pain have rarely been reported, even when administration was abruptly discontinued. There have been a few reports of dependence with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

For Continuing Postsurgical Pain Control

Talwin® HCl 50 mg.
brand of · equivalent to 50 mg. base
pentazocine HCl tablets, NF

1 or 2 tablets every three or four hours

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

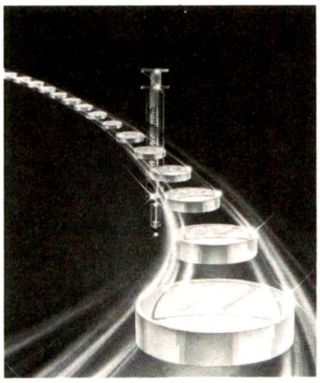
Potent—Dependable—Nonopiate

Talwin® HCl 50 mg.

brand of pentazocine HCl tablets, NF. equivalent to 50 mg. base

Relieves pain of a moderate to severe nature.

Usual initial adult dose is 1 tablet every 3 or 4 hours.



Please consult full prescribing information before prescribing. A summary follows:
Talwin HCl is intended for the relief of moderate to severe pain. One 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. Talwin is a weak narcotic antagonist with sedative activity.

Contraindication

Hypersensitivity to pentazocine.

Warnings

Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin HCl should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions

Oral Talwin has been rarely reported to cause respiratory depression. It should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

Adverse Reactions

Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations; and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, paresthesia, toxic epidermal necrolysis.

Dosage and Administration

Adults: The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg. Tolerance is rare. Abrupt discontinuance following chronic use has rarely caused withdrawal symptoms.

Overdosage

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

References

1. Kay B: A clinical comparison of orally administered aspirin, dextropropoxyphene and pentazocine in the treatment of postoperative pain. *J Int Med Res* 2:149-152, 1974.
2. AMA Department of Drugs: *AMA Drug Evaluations*, ed 3. Littleton, Mass, Publishing Sciences Group, Inc, 1977, pp 327-328.

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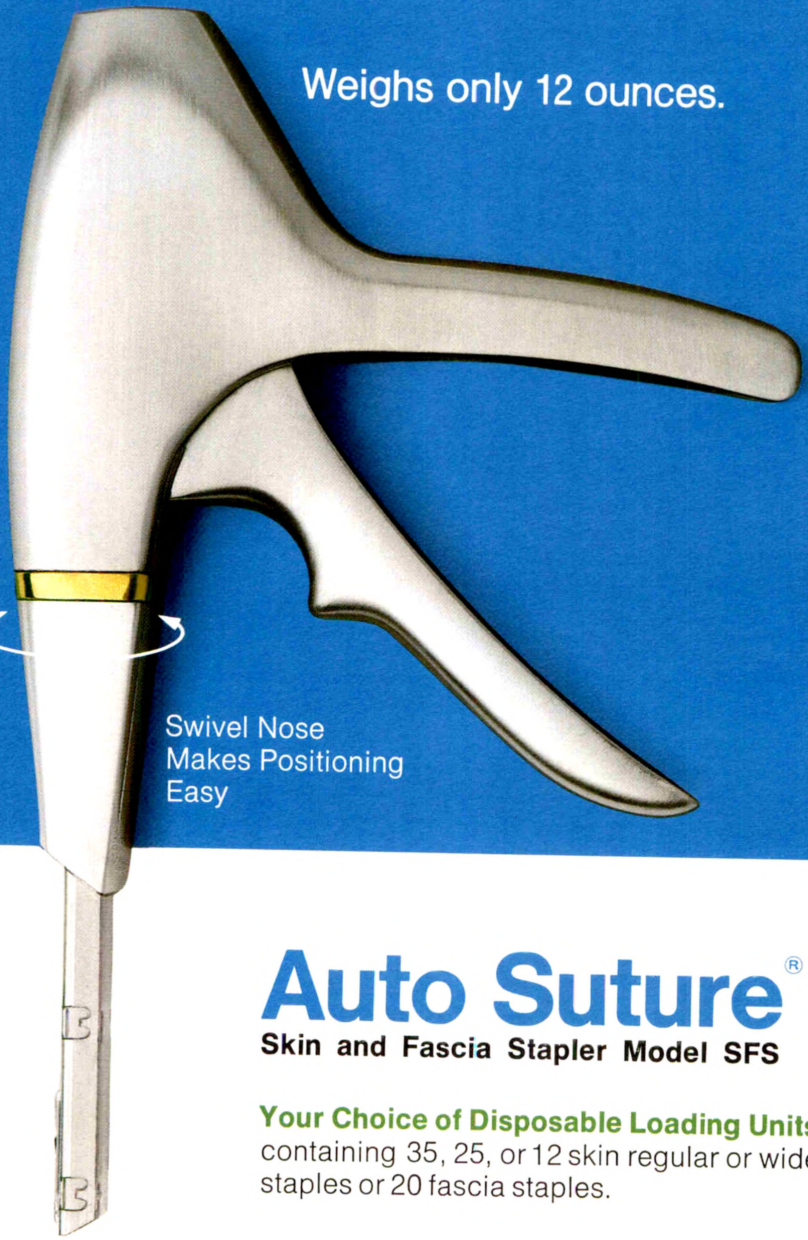

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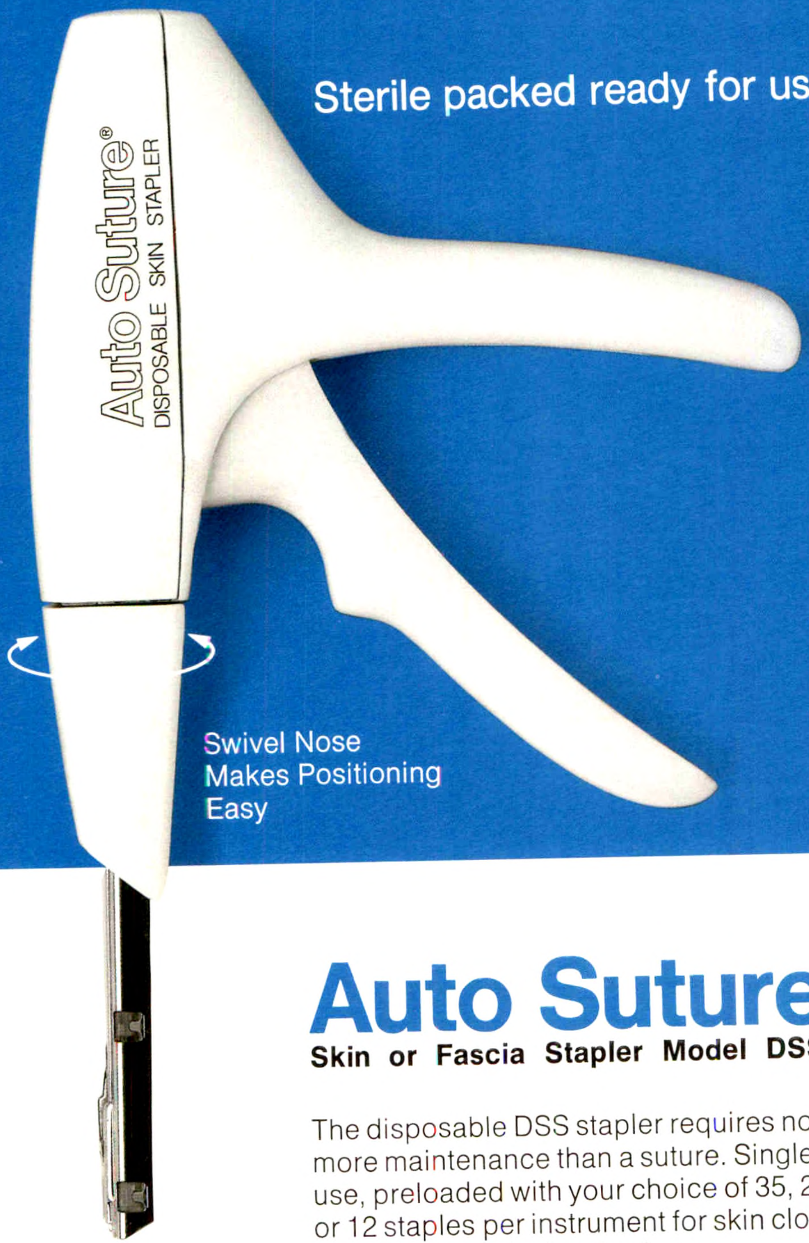

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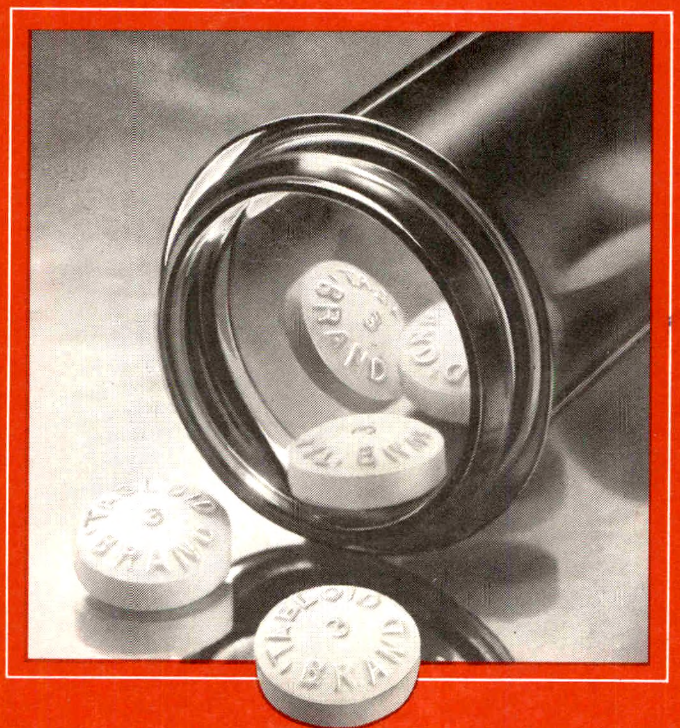

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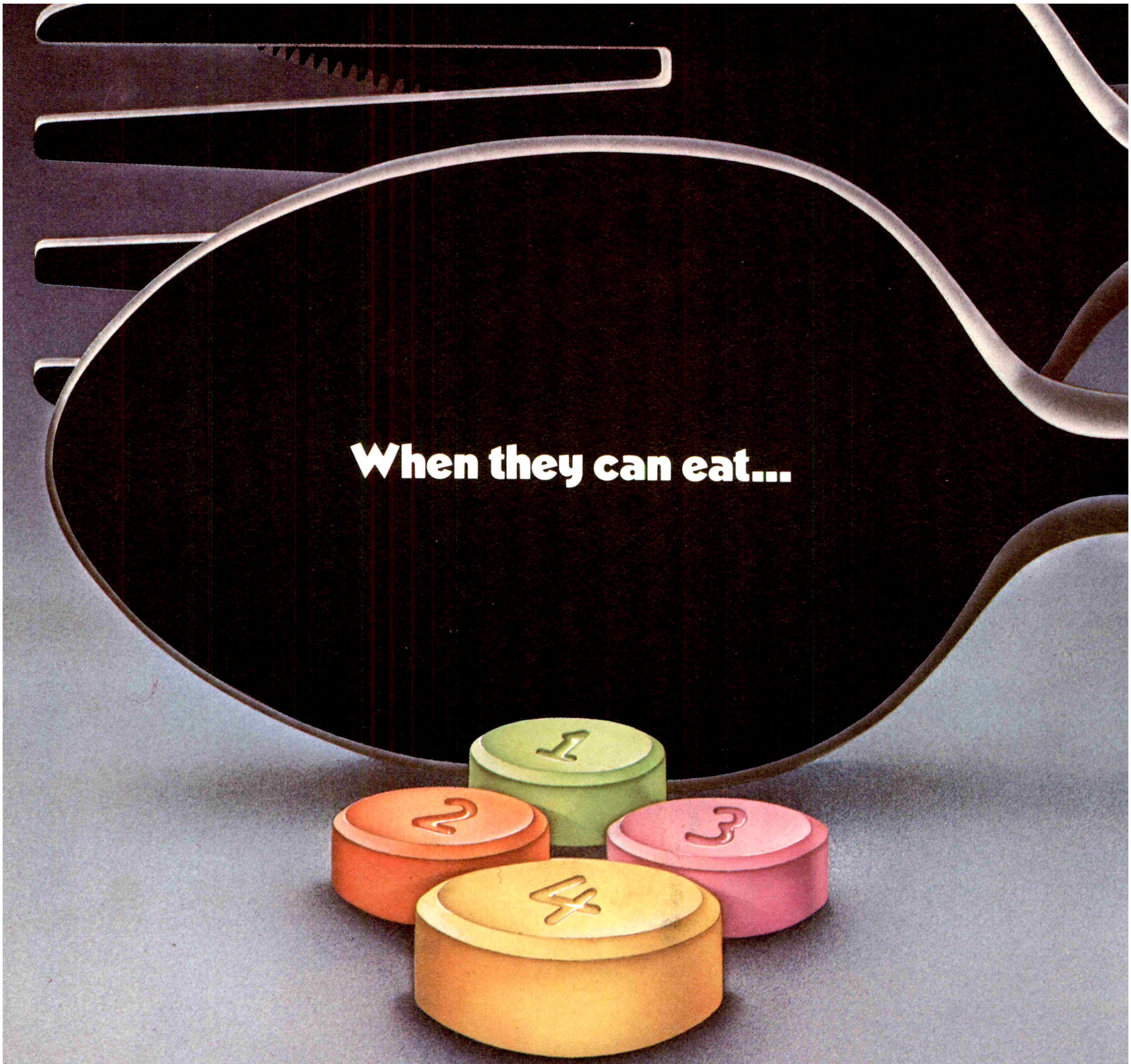

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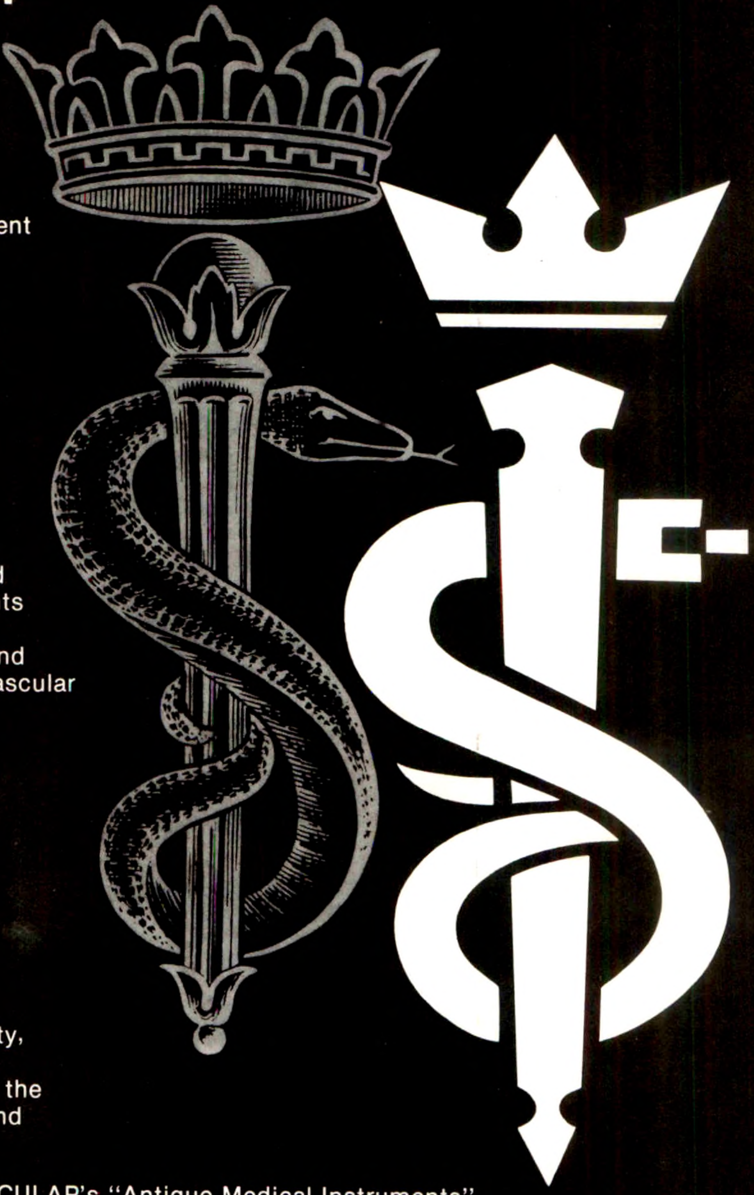

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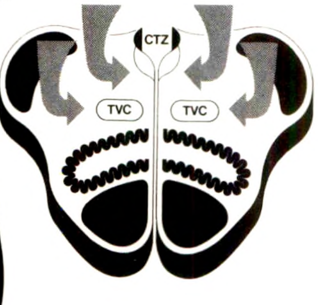
2) against emetic sights, emotions, and organ insults (at the TVC)

In using Torecan, the physician should consider the adverse reactions which are associated with the drug specifically and phenothiazines generally.**

- It's not for sedative use.
- It's not intended as a tranquilizer.
- It's not an antihistamine.
- It's not intended for psychotic symptoms.

*As shown in animal studies; TVC—True Vomiting Center, CTZ—Chemoreceptor Trigger Zone.

**Please see brief summary for detailed information concerning potential adverse reactions.



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Torecan® (thiethylperazine)
Tablets, Suppositories and Injection

Contraindications: Severe CNS depression, comatose states, and in patients who have demonstrated a hypersensitivity to phenothiazines (e.g., blood dyscrasias, jaundice). Because severe hypotension has been reported after the intravenous administration of phenothiazines, this route of administration is contraindicated. The drug is contraindicated in pregnancy.

Warnings: Phenothiazines are capable of potentiating CNS depressants as well as atropine and phosphorous insecticides. The drug may impair mental and/or physical ability required in the performance of potentially hazardous tasks such as driving a car or operating machinery.

Postoperative Nausea and Vomiting: When used to control postoperative nausea and vomiting in patients undergoing elective surgical procedures, restlessness and postoperative CNS depression during anesthesia recovery may occur. Possible postoperative complications of a severe degree of any of the known reactions of this class of drug must be considered. Postural hypotension may occur after an initial injection, rarely with the tablet or suppository. Do not use with epinephrine in the treatment of drug-induced hypotension as phenothiazines may induce a reversed epinephrine effect. The most suitable vasoconstrictor agents are levarterenol and phenylephrine. The use of Torecan has not been studied following intracardiac and intracranial surgery. Not recommended for use in children under 12 years of age, or in nursing mothers since safety and efficacy have not been established.

Precautions: Convulsions and abnormal movements such as extrapyramidal symptoms have occurred. The varied extrapyramidal symptom complex is more likely to occur in young adults and children. Extrapyramidal effects must be treated by reduction of dosage or cessation of medication. For treatment of nausea and/or vomiting associated with anesthesia and surgery, the drug should be administered by deep intramuscular injection at or shortly before the termination of anesthesia.

Adverse Reactions: CNS: convulsions, extrapyramidal symptoms such as dystonia, torticollis, oculogyric crisis, akathisia and gait disturbances, occasional cases of dizziness, headache, fever and restlessness have been reported. Drowsiness may occur initially on injection but is usually alleviated by a reduction in dosage. Dryness of the mouth and nose, blurred vision, tinnitus; sialorrhea and altered gustatory sensation. Peripheral edema of the arms, hands and face. Cholestatic jaundice; cerebral vascular spasm and trigeminal neuralgia have been reported occasionally. The following have occurred with phenothiazine derivatives and should be considered: agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia, pancytopenia, eosinophilia, leukocytosis; miosis, obstipation, anorexia, paralytic ileus; erythema, exfoliative dermatitis and contact dermatitis; jaundice, biliary stasis. Hypotension, rarely leading to cardiac arrest; ECG changes. Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia, some of which have persisted for several months or years especially in patients of advanced age with brain damage. Menstrual irregularities, altered libido, gynecomastia, weight gain; false positive pregnancy tests. Urinary retention, incontinence; fever, laryngeal edema and angioneurotic edema, asthma. Hyperpyrexia, behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. ECG changes. While there is no evidence that ECG changes are in any way precursors of any significant disturbance of cardiac rhythm, sudden and unexpected deaths apparently due to cardiac arrest have been reported in a few instances in hospitalized psychotic patients previously showing characteristic ECG changes. A peculiar skin-eye syndrome, which is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea, has also been recognized as a side effect following long-term treatment. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported.

Drug Interactions: Phenothiazines are capable of potentiating CNS depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorous insecticides. The drug may induce a reversed epinephrine effect on occasion.

For complete details, please see full prescribing information.

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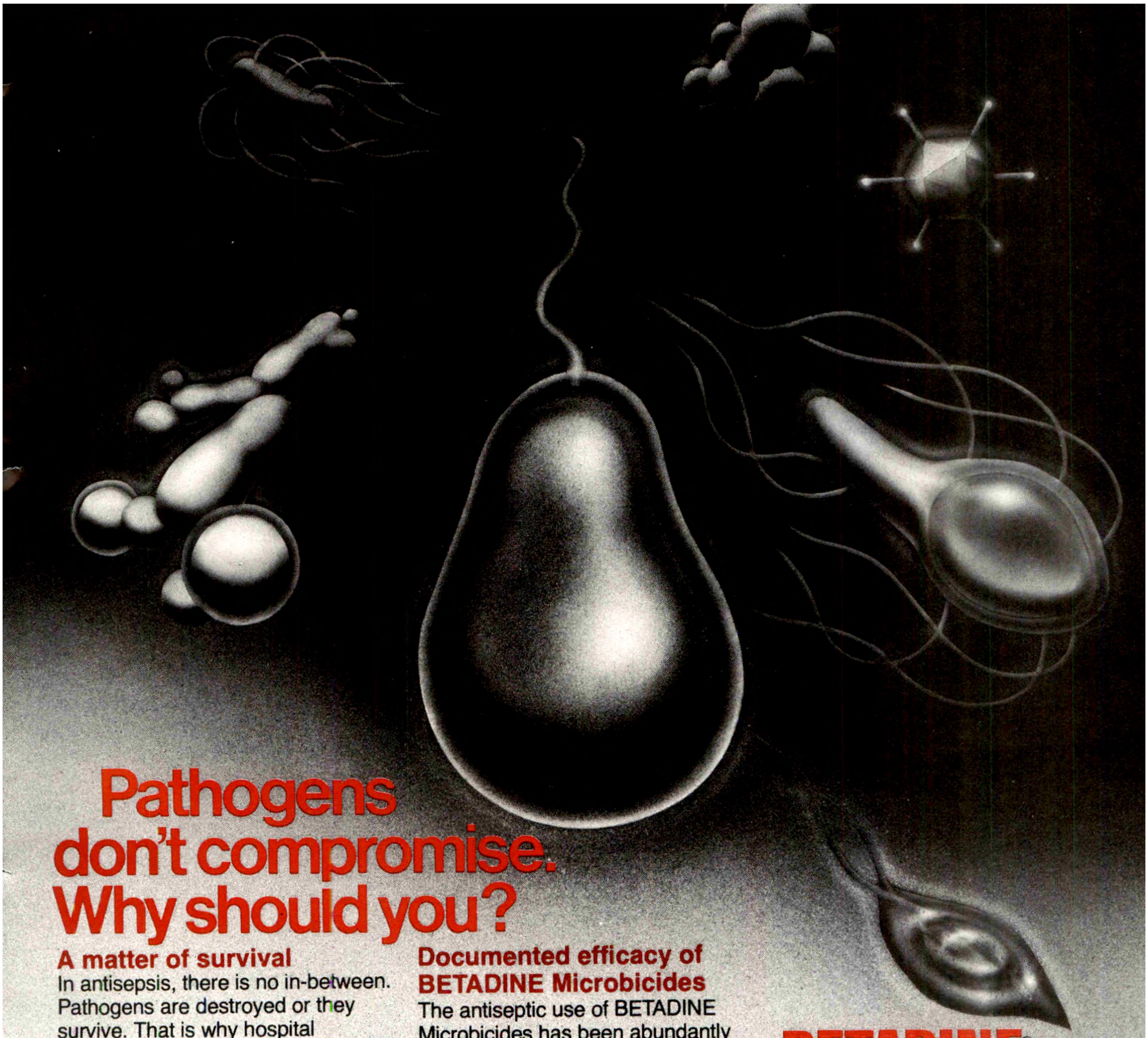

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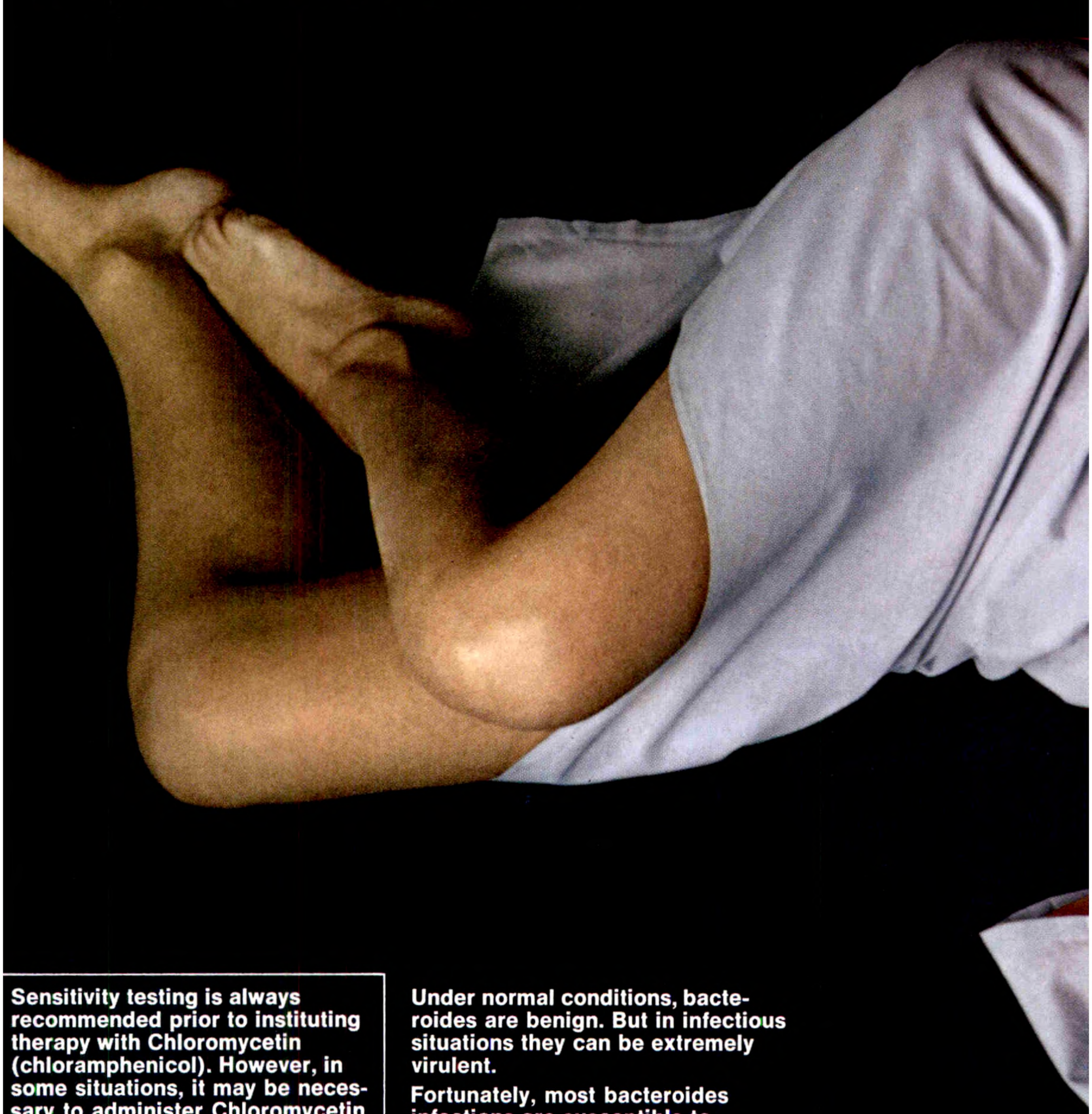
Illustration is artist's representation of organisms.

- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena



Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for

drugs are ineffective or contraindicated.

But when bacteroides are
cated, Chloromycetin (chl
phenicol) therapy may wel
conservative course. For, i
situations, the benefits-to-
with Chloromycetin is very f

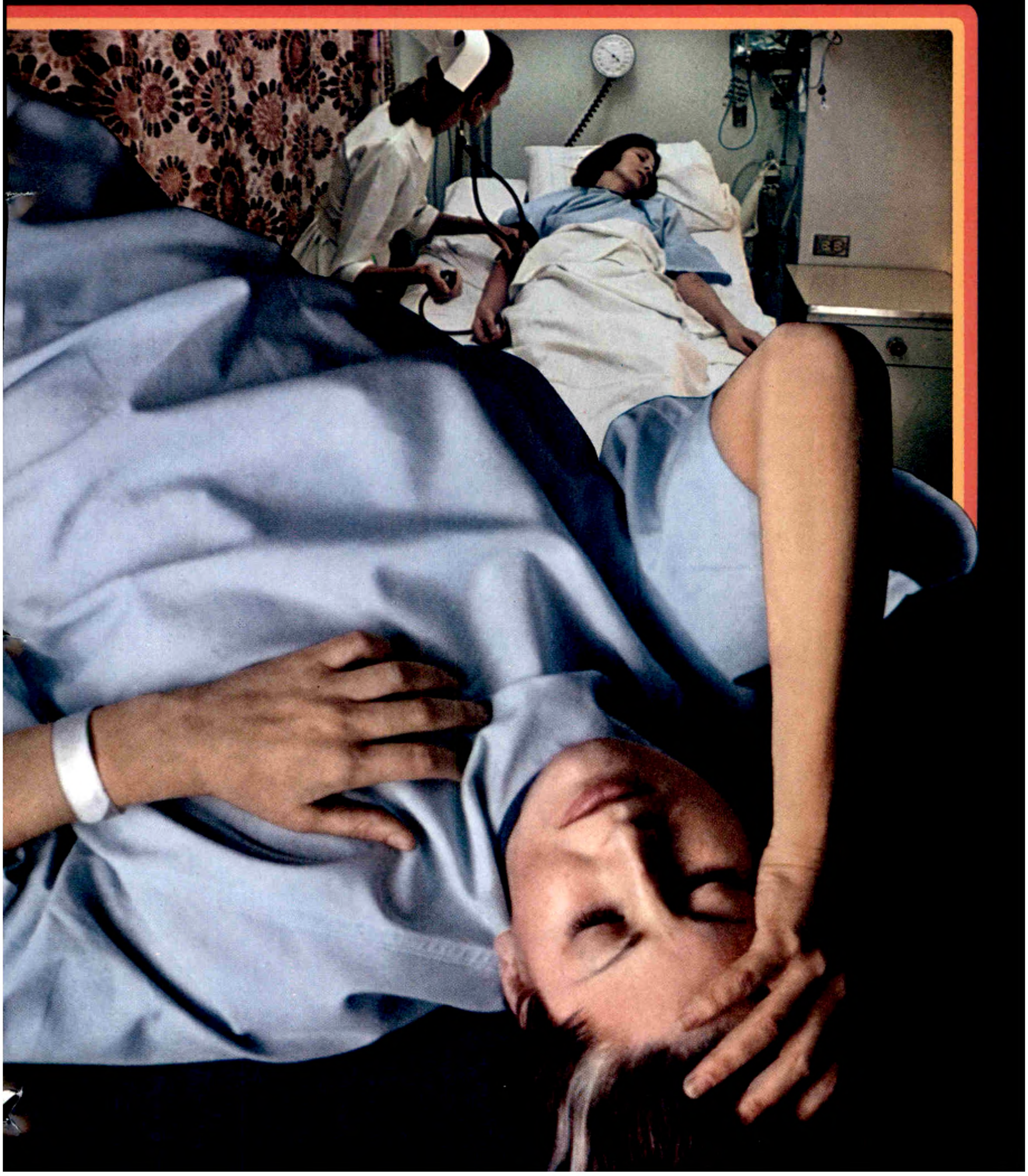
See next page for full presc

Bacteroides...

often an indication for

CHLOROMYCETIN®

(chloramphenicol) Sodium Succinate



Prescribing Information—Chloromycetin
(chloramphenicol) Sodium Succinate
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae.* It is particularly active against *Salmonella typhi* and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**

   It is not recommended for the routine treatment of the typhoid carrier state.
2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.
   - a) *Salmonella* species
   - b) *H influenzae*, specifically meningeal infections
   - c) Rickettsia
   - d) Lymphogranuloma-psittacosis group
   - e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   - f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
  - (1) abdominal distension with or without emesis;
  - (2) progressive pallid cyanosis;
  - (3) vasomotor collapse, frequently accompanied by irregular respiration;
  - (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

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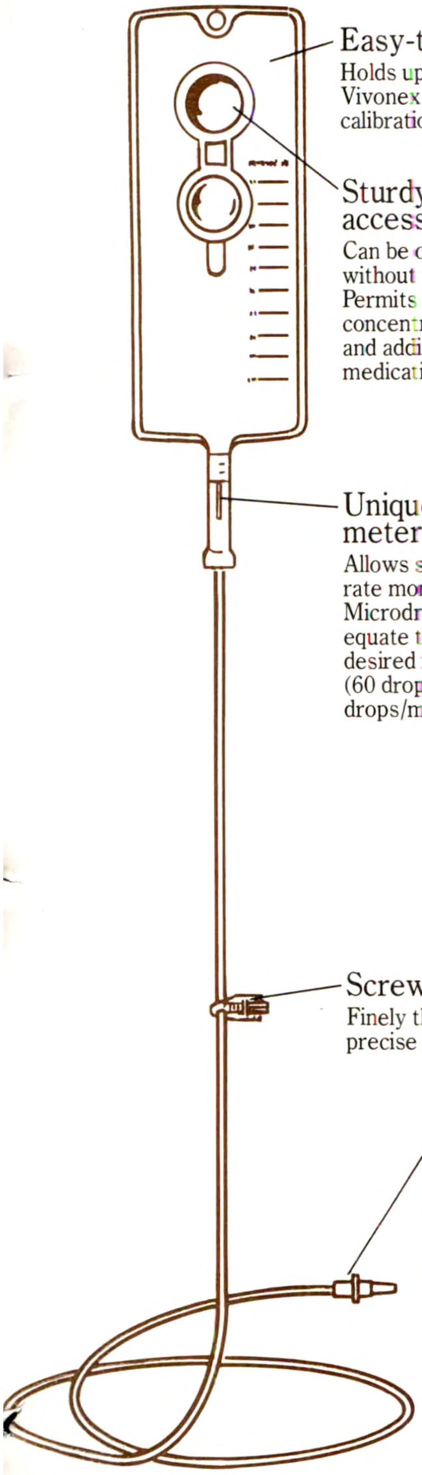

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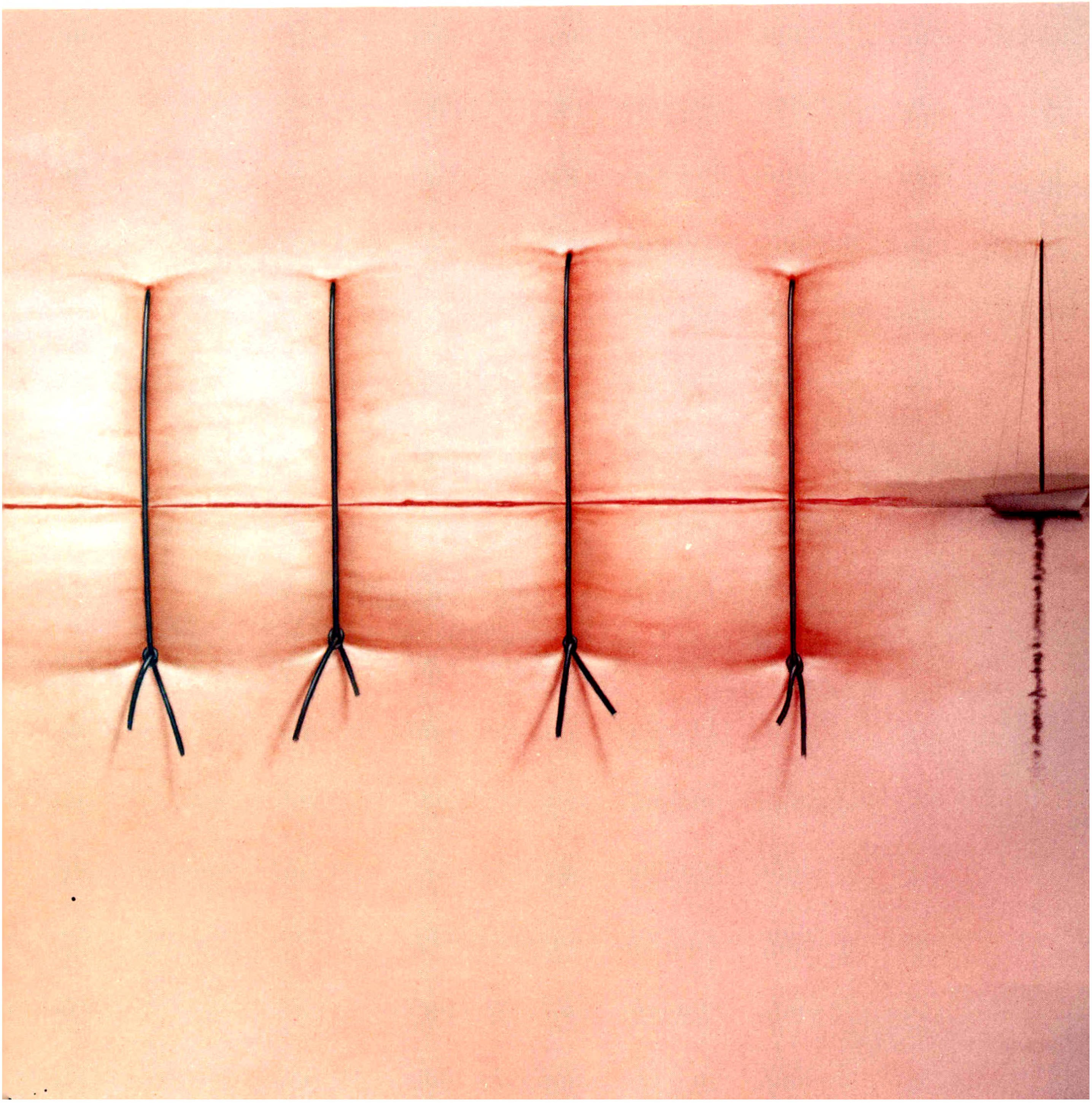

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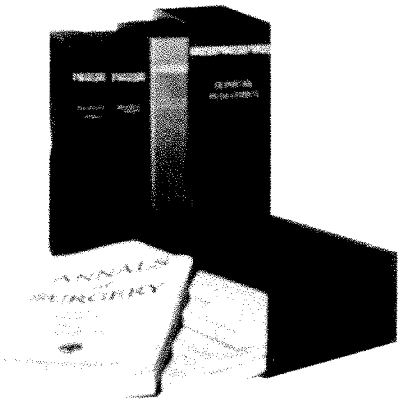

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Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
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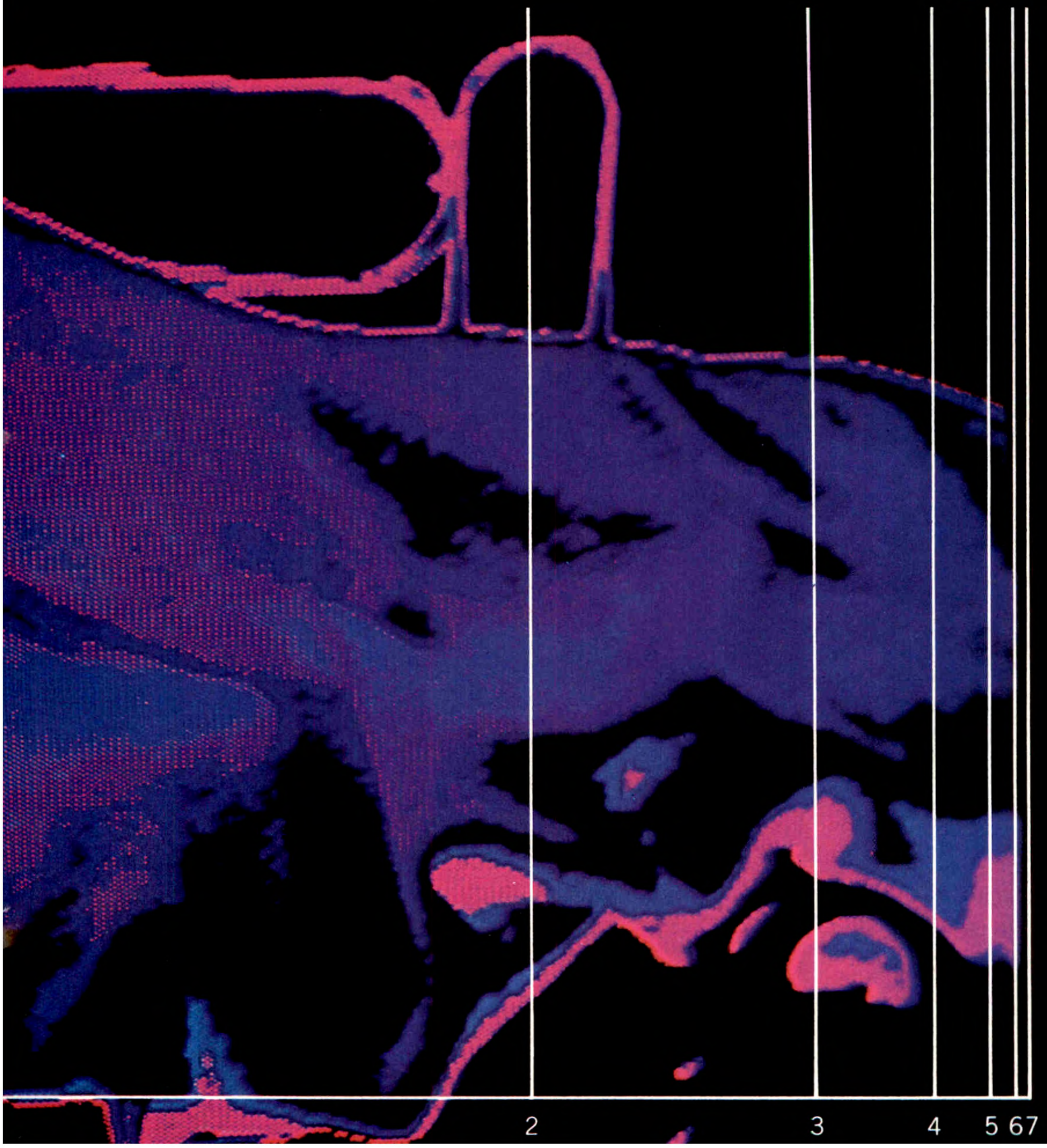

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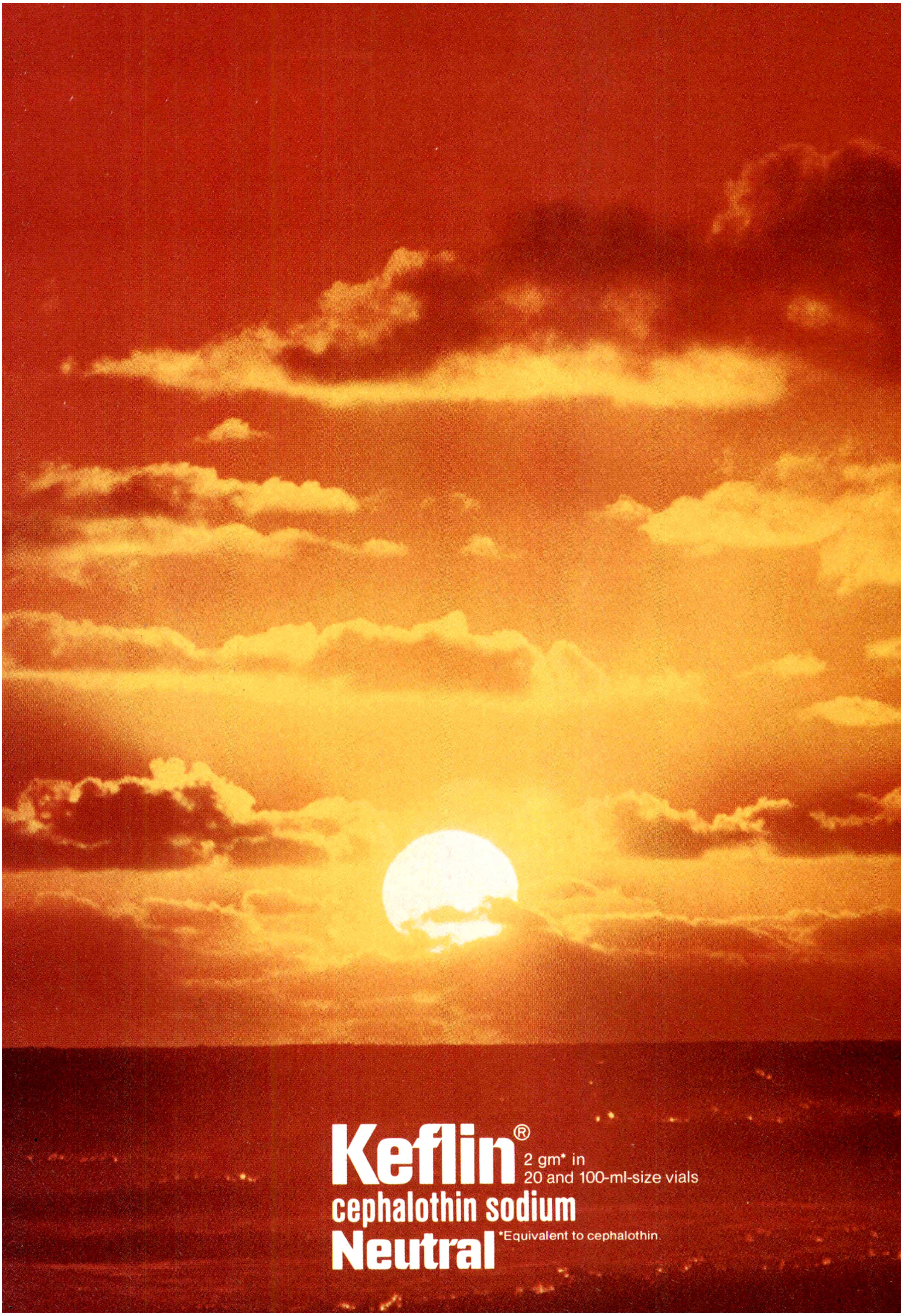

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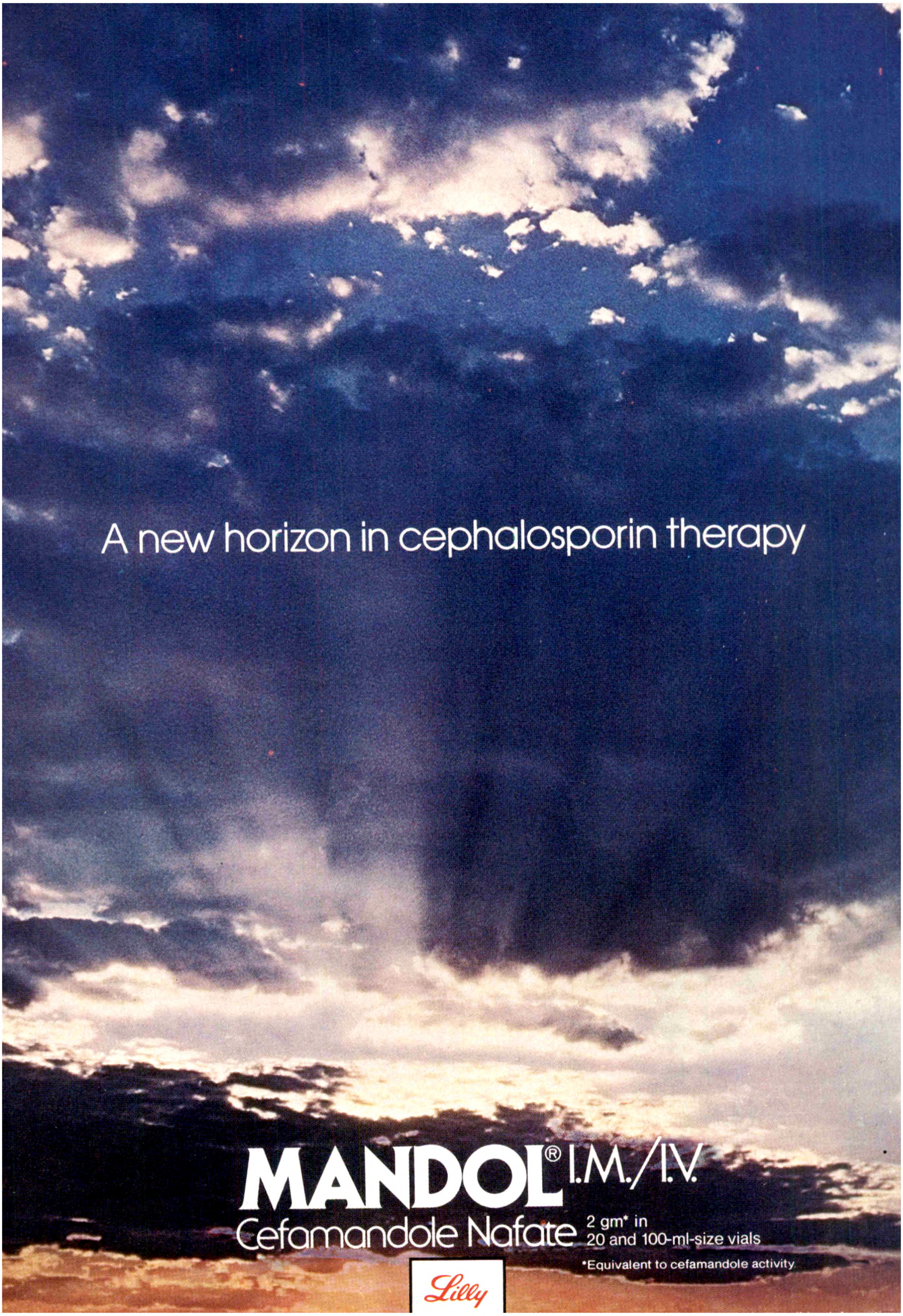
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Indications and Usage: Mandol is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, *Klebsiella* species, *Staphylococcus aureus* (penicillinase and non-penicillinase-producing), beta-hemolytic streptococci, and *Proteus mirabilis*

Urinary tract infections caused by *Escherichia coli*, *Proteus* species (both indole-negative and indole-positive), *Enterobacter* species, *Klebsiella* species, group D streptococci (*Note:* Most enterococci, e.g., *S. faecalis*, are resistant), and *S. epidermidis*

Peritonitis caused by *E. coli* and *Enterobacter* species

Septicemia caused by *E. coli*, *S. aureus* (penicillinase and non-penicillinase-producing), *S. pneumoniae*, *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, and *Klebsiella* species

Skin and skin-structure infections caused by *S. aureus* (penicillinase and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, *E. coli*, *Enterobacter* species, and *P. mirabilis*

Clinical microbiologic studies in nongonococcal pelvic inflammatory disease in females, lower respiratory infections, and skin infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Mandol has been used successfully in these infections in which several organisms have been isolated. Most strains of *Bacteroides fragilis* are resistant in vitro; however, infections caused by susceptible strains have been treated successfully.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefamandole. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Mandol may be used concomitantly with an aminoglycoside (*see* Precautions). The recommended doses of both antibiotics may be given, depending on the severity of the infection and the patient's condition. The renal function of the patient should be carefully monitored, especially if higher dosages of the antibiotics are to be administered.

Antibiotic therapy of beta-hemolytic streptococcal infections should continue for at least ten days.

Contraindication: Mandol is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY WITH MANDOL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

In newborn infants, accumulation of other cephalosporin-class antibiotics (with resulting prolongation of drug half-life) has been reported.

Precautions: Although Mandol rarely produces alteration in kidney function, evaluation of renal status is recommended, especially in seriously ill patients receiving maximum doses.

Prolonged use of Mandol may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly). There may be a false-positive test for proteinuria with acid and denaturization-precipitation tests.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infancy—Mandol has been effectively used in this age group, but all laboratory parameters have not been extensively studied in infants between one and six months of age; safety of this product has not been established in prematures and infants under one month of age. Therefore, if Mandol is administered to infants, the physician should determine if the potential benefits outweigh the possible risks involved.

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, eosinophilia, and drug fever have been reported. These reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Neutropenia and thrombocytopenia have been reported rarely. Some individuals have developed positive direct Coombs tests during treatment with the cephalosporin antibiotics.

Liver—Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been noted.

Kidney—Decreased creatinine clearance has been reported in patients with prior renal impairment. As with some other cephalosporins, transitory elevations of BUN have occasionally been observed with Mandol; their frequency increases in patients over 50 years of age. In some of these cases, there was also a mild increase in serum creatinine.

Local Reactions—Pain on intramuscular injection is infrequent. Thrombophlebitis occurs rarely.

Administration and Dosage: *Dosage—Adults:* The usual dosage range for cefamandole is 500 mg to 1 gm every four to eight hours.

In infections of skin structures and in uncomplicated pneumonia, a dosage of 500 mg every six hours is adequate.

In uncomplicated urinary tract infections, a dosage of 500 mg every eight hours is sufficient. In more serious urinary tract infections, a dosage of 1 gm every eight hours may be needed.

In severe infections, 1-gm doses may be given at four to six-hour intervals.

In life-threatening infections or infections due to less susceptible organisms, doses up to 2 gm every four hours (i.e., 12 gm per day) may be needed.

Infants and Children: Administration of 50 to 100 mg/kg/day in equally divided doses every four to eight hours has been effective for most infections susceptible to Mandol. This may be increased to a total daily dose of 150 mg/kg (not to exceed the maximum adult dose) for severe infections. (*See* Warnings and Precautions for this age group.)

Note: As with antibiotic therapy in general, administration of Mandol should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained; a minimum of ten days of treatment is recommended in infections caused by group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment for several weeks; and doses smaller than those indicated above should not be used.

Impaired Renal Function—When renal function is impaired, a reduced dosage must be employed and the serum levels closely monitored. After an initial dose of 1 to 2 gm (depending on the severity of infection), a maintenance dosage schedule should be followed (see chart). Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

MAINTENANCE DOSAGE GUIDE FOR PATIENTS WITH RENAL IMPAIRMENT

Creatinine Clearance (ml/min/1.73 m²)	Renal Function	Life-Threatening Infections—Maximum Dosage	Less Severe Infections
>80	Normal	2 gm q 4 h	1-2 gm q 6 h
80-50	Mild Impairment	1.5 gm q 4 h OR 2 gm q 6 h	0.75-1.5 gm q 6 h
50-25	Moderate Impairment	1.5 gm q 6 h OR 2 gm q 8 h	0.75-1.5 gm q 8 h
25-10	Severe Impairment	1 gm q 6 h OR 1.25 gm q 8 h	0.5-1 gm q 8 h
10-2	Marked Impairment	0.67 gm q 8 h OR 1 gm q 12 h	0.5-0.75 gm q 12 h
<2	None	0.5 gm q 8 h OR 0.75 gm q 12 h	0.25-0.5 gm q 12 h

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males:}\quad \frac{\text{Weight (kg)} \times (146 - \text{age})}{72 \times \text{serum creatinine}}$$

$$\text{Females:}\quad 0.9 \times \text{above value}$$

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ANNALS OF SURGERY

Vol. 188 December 1978 No. 6

Clinical Correlates of Resectability and Survival in Gastric Carcinoma

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The course of 201 patients with carcinoma of the stomach treated from 1962 through 1966 was followed with 97% determinacy for 10 years. The actual five year survival rate was 11%; the ten year rate was 7%. The mean duration of survival was 5.8 ± 2.7 (S.D.) months. These results were similar to those reported for the period 1922–1926. Survival was strongly correlated with the surgeon's assessment after exploration. All patients alive after five years had operations thought to be curative, usually partial gastrectomies; the survival rate of this group was 24%. Gastroenterostomy was ineffectual palliation. Better results will require nonsurgical adjuncts, since the correlates of survival are those of minimally invasive cancer.

At the time the results of treatment for gastric carcinoma at this hospital from 1922 through 1926 were reviewed,[15] carcinoma of the stomach was the most frequent cause of death from cancer in men and was exceeded in women only by cancers of the breast and uterus. Although its attack rate declined in the subsequent years represented by more recent reports,[16,27,28] gastric carcinoma even now is the fifth most frequent cause of deaths from malignant disease in men and eighth in women.[17,21]

During the same period the attack rate has decreased, however, the five year survival rates among all patients treated in general hospitals have stayed remarkably constant, at about 11%.[14] The rate may be higher at some referral centers and lower at hospitals specializing in cancer.[10,18,22,23] The salvage rate is stable irrespective of whether patients are treated by limited gastrectomy or by radical gastrectomy with removal of adjacent organs.

The problem for the surgeon dealing with an individual patient today is, first, to be able to predict chances of spread and of survival from preoperative clues and, second, to select the proper operation depending on the likelihood of cure or palliation, given the situation found when the abdomen is opened. Distal gastrectomy is most likely to cure small polypoid or ulcerative gastric cancers with an "intestinal" (glandular) histologic pattern and without lymphatic metastases than cancers of other types.[4,9,25,29] But the choice of operations for both these cancers and cancers of other kinds in other locations is always a matter of judgment. Proximal and total gastrectomies may be curative for adenocarcinomas near the gastroesophageal junction even when regional lymph nodes are involved with cancer, provided that the resection margins are free of cancer.[1,24] We describe the influence of preoperative findings and of other operative discoveries on prognosis in patients followed for ten years or until their earlier death.

Methods

Records were analyzed of all patients with proved carcinoma of the stomach who were discharged from January 1, 1962 through December 31, 1966. The status of 97% of these patients was known in 1976. Variables were tested for significance by χ^2, γ, and R (correlation) methods.

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Supported in part by the Henry Greco Fund.

Submitted for publication: December 20, 1977.

0003-4932/78/1200/0711 $00.75 © J. B. Lippincott Company

Results

Among 201 patients the ratio of men to women was nearly 2:1 (132:69). The ages of 82% were from 50 to 80 years.

Group A blood was present in 40%. There was a family history of gastric cancer in 10%, and 3.5% had pernicious anemia. Abdominal pain was the major complaint in 52%. Hospital attention was sought by 55% within three months of the onset of their symptoms.

A palpable abdominal mass was present in 24%. Occult blood was identified in the stool of 68% of 157 patients tested; achlorhydria was found in 76% of 68 tested. Barium-contrast roentgenograms of the stomach were 93% diagnostic. Of 61 gastroscopic biopsies, 80% showed carcinoma.

Operations were performed on 93% of the 201 patients. Cancers arose in the gastric body or antrum in 73%. No cancers arose in gastric remnants after gastrectomies for ulcer. Only 19% of cancers seen at the operating table were limited to the stomach. Regional lymph nodes contained cancer in 76% of patients who were operated upon. Peritoneal metastases were present in 34%, and hepatic metastases were present in 20%.

The incidence of adenocarcinoma was 76%, of undifferentiated carcinoma 17%, and of signet-cell carcinoma 6%. Depth of penetration was recorded for 127 specimens. In 83% it was through all layers of the gastric wall; in only 4% was it limited to the mucosa.

Cancers were resected in 70% of patients operated upon (Table 1), and in 48% of resections all gross neoplasm was removed. Total gastrectomies (27% of resections) almost always involved en-bloc removal of the spleen, pancreatic tail, and omenta.

Fatality rates while the patients were hospitalized were 10% for gastric resection, 37% for bypass, and 28% for diagnostic laparotomy or no operation. The overall actual five year survival rate was 11%. The overall actual ten year survival rate was 7%. The mean duration of survival of all patients was 5.8 ± 2.7 (S.D.) months. Table 1 shows survival statistics for each form of treatment.

Correlations

Despite apparently unfavorable patterns of disease in women, results of treatment were the same as for men. A palpable mass was found in 43% of women vs. 14% of men ($p < 0.001$). Regional lymphatic metastases were present in 91% of women vs. 69% of men ($p = 0.004$). Only 7% of patients with a palpable mass had cancer localized to the stomach ($p = 0.003$). Nonetheless, the five year survival rates of 13% for women and 7% for men were not significantly different ($p = 0.33$).

Although old age was an ominous variable, no importance can be attributed to this correlation without matched or life-table controls. Of 20 patients over 80-years-old, only one survived longer than three years ($p < 0.001$). The operative fatality rate of this group was 35% as compared with 5% in patients under 50 years old ($p = 0.001$).

No correlation existed between the duration of symptoms and survival. Nonetheless, all seven patients who were asymptomatic survived longer than six months, and four of them survived over three years ($p < 0.01$).

Rarely was distant cancer present unless the regional lymph nodes also contained cancer. In general the sequence was involvement of regional lymph nodes, then adjacent organs, and, last, peritoneal surfaces. There were lymphatic metastases in 96% of 81 patients with extension beyond the stomach.

Survival was closely related to the status of perigastric organs. Of 31 patients not having lymphatic metastases, 45% survived five years, but only 8% of 100 patients recorded with metastases in the lymph nodes lived that long ($p < 0.001$). Of 35 patients not having adjacent organs invaded, 31% survived five years, but only 7% of 91 patients ($p < 0.001$) with local invasion and lymph-node involvement.

Peritoneal or hepatic metastases were even more ominous. Survival longer than 12 months occurred in

TABLE 1. *Treatment and Survival*

	Patients No.	Median Survival Months	5-Year Survival %
Partial gastrectomy	106	17.	17
Total gastrectomy	25	8.5	16
Gastroenterostomy	19	1.8	0
Exploratory laparotomy	37	2.6	0
No exploration	14		
Total	201	Mean 5.8 ± 2.7 (S.D.)	Mean 11

but 16% of 63 patients with peritoneal metastases ($p < 0.01$) and 8% of 37 with hepatic metastases ($p < 0.001$). However, four patients (6%) with omental metastases not grossly apparent survived at least five years after omentectomy.

Extra-abdominal metastases in the low mediastinum were chiefly from cancers at the esophagogastric junction (57% of 14 instances ($p < 0.001$)). They were associated with a worse prognosis than intra-abdominal metastases, as no patient with mediastinal metastases survived five years.

Neither the location of the primary tumor nor its extragastric extension were necessarily contraindications to resection. When metastases were limited to the perigastric lymph nodes, 97% of 80 patients had resections, but even 43% (39) of 91 patients with widespread cancer underwent resection. Cancers at the esophagogastric junction were especially amenable to resection, inasmuch as 86% of 22 patients with cancer there had the primary cancer removed, as compared with 63% of the entire group of 187 patients operated upon ($p < 0.001$).

The surgeon's assessment after exploration was strongly correlated ($p = 0.004$) with survival. All 22 patients surviving five years were among the 92 (46% of the total population studied) who had operations deemed potentially curative. Therefore, the five year survival rate of patients operated upon for cure was 24%. Only one patient operated upon for diagnostic reasons survived over one year, and only two who had palliative operations survived between three and five years.

Characteristics of the neoplasm itself were prognostic. Ulcerating cancers (58 cases) were more favorable than polypoid (60 cases); they were present in 67% of the 15 patients who survived at seven years ($p = 0.006$)—the shallower the invasiveness, the better. Among 22 patients with neoplasms confined by the submucosal layer, the five year survival rate was 41% ($p < 0.001$). Undifferentiated cancers were notably aggressive; among 34 patients 53% were inoperable or unresectable ($p = 0.02$), and this cell type was most commonly associated with hepatic metastases ($p < 0.003$).

Gastrojejunostomy was an ineffectual means of palliation. Even resection was rarely helpful for relief of symptoms. Only one of 17 patients was relieved of symptoms after a bypass, and only 29% of 45 patients were relieved with a palliative resection. The persistence of symptoms was invariably followed by death within two years in 79 patients.

Recurrences after resection were frequent, and they were almost always followed by death. Recurrences appeared even after five years without evidence of cancer. They affected 36% of the 22 patients alive at five years, leaving but 14 of the original 201 patients alive at ten years. Characteristics of the survivors are shown in Table 2. No second-look operations were done.

TABLE 2. *Correlates of Survival in 5-Year Survivors ($N = 22$)*

	p value
Asymptomatic	0.006
No mass	0.03
Non-diagnostic G.I. series	0.04
Gastric acid	0.03
No extension to other organs	<0.001
Negative lymph nodes	<0.001
No hepatic metastases	0.01
Few lymph nodes involved	<0.001
Negative resection margins	0.006
Invasion only to muscularis	<0.001
No recurrence	<0.001

Discussion

Forty years later the course of patients in this hospital with gastric cancer has changed very little, although the overall five year survival rate has gone from 4–11%, but the conclusions of the first report[15] could apply almost unchanged to the present group. To be sure, the rate of resectability of 223 patients admitted from 1922 to 1926 under the care of nine surgeons was only 60% as compared with a 93% rate of resectability in 201 patients from 1962 to 1966 under the care of dozens of staff and resident surgeons. Nonetheless, the hospital fatality rates were similar after diagnostic laparotomy (37% vs. 28%) and after palliative bypass (28% vs. 37%); they were different only after gastric resections (38% vs. 10%) ($p < 0.001$). Lower fatality rates after gastrectomy were first noted for the period 1942–1946. When the higher operative fatality rate in the early series is considered, the apparent increase in the overall five year survival rate from 4 to 11% is probably mostly a result of improved surgical care in general; the introduction of total gastrectomy in 1932 may have had a slight positive effect as well. Surely there has been no improvement in five year survival rates after gastric resection when postoperative deaths are excluded: 24% then, 15% now. Bias introduced by the 38% postgastrectomy fatality rate in the early series was a major element in producing a 20% five year survival rate in patients who survived gastric resection.

Similarities in the period 1947–1952,[28] when the postgastrectomy fatality rate was about the same as in 1962–1966, provide another historical control. The overall five year survival rates were the same (13% vs. 11%), the same after all resections (19% vs. 17%), and the same after all resections for cure (28% vs. 24%).

The bright spot in both the 1947–1952 series and the present series was the 47% five year survival rate in patients who underwent distal gastrectomy for cure (vs. 20% in 1922–1926). These patients clearly represent the best prospects for cure.[3,4,9,22]

Besides the similarities in results of treatment in the present group as compared with those from earlier decades in this hospital, similarities of other variables with those in other published reports far outweigh differences. Similarities include sex ratio, presence of an abdominal mass, and location of neoplasms. Undifferentiated and deeply penetrating primary cancers and the presence of blood vessel invasion and of lymphatic, hepatic, and peritoneal metastases are all dire events[2–4, 7–9,22,25,29] Whether polypoid or ulcerating neoplasms have intrinsic biological properties affecting lethality is a problem better argued elsewhere.

Although the duration of symptoms was not a prognostic factor, absence of symptoms was positive for survival. There would seem to be two implications from these facts: 1) By the time symptoms occur, gastric cancer has reached a state at which metastases occur, and 2) only gastroscopic screening programs that diagnose superficial or preinvasive cancer are likely to decrease the mortality rate of carcinoma of the stomach. In view of the low yield at high cost and with a modicum of risk, gastroscopic screening programs cannot be recommended for this country at present. Their use should be limited to countries in which the attack rate of gastric cancer is high.[11,30] Even if an arguable increase in "stump cancer" years after gastrectomy for ulcer disease is confirmed,[6,13,20] economic considerations would not support routine endoscopic examination of this group of patients in view of the low expectation of yield.

The implications of better survival in the presence of gastric acid are unclear. Because we did not record the size of the cancers, no statement can be made about the amount and location of stomach uninvolved with neoplasm in patients who had free acid. If the amount of stomach involved with cancer is not an inverse correlate of free acid, there would be several paths of speculation—such as whether cancers of greater virulence inhibit acid production or whether the degree of malignancy is greater in cancers arising in a field of cells that do not secrete acid.

The data emphasize the propensity for late recurrences in gastric cancer, as in breast cancer and melanoma.[22] An incidence of about 12% have been reported by others,[5,10] and we lost 36% of our patients alive at five years within the next five years. We have one patient with pernicious anemia who died with recurrent cancer 17 years after a total gastrectomy.

Since vigorous x-ray therapy and chemotherapy were not available for our patients during the years covered by this survey, no conclusions about their efficacy can be drawn from our data. Adjunctive Thio-TEPA or FUDR were not helpful in the cooperative trial of the Veterans Administration.[22] However, the combination of 5-FU with adriamycin and methyl lomustine or mitomycin C may be beneficial for treatment of residual disease in perhaps 20% of patients with gastric carcinoma.[19,*]

Recommendations for Therapy

Our recommendations for treatment of gastric cancer are these:

1) Fiberoptic gastroscopic biopsy should be obtained when the presence of cancer, as opposed to benign ulcer, would change the operative plan. If the biopsy specimen does not contain cancer, it will not influence the operative program, but, if it does, it will facilitate the operation. Lymphomas that could be removed only by a total gastrectomy might be treated better with radiation than with surgery.

2) Patients fit for an operation should be explored with a view to resection. Only resection carries any hope of cure. Even if it does not cure, it is much more effective in relieving symptoms than gastric bypasses. Removal of tumor bulk may potentiate the effects of adjunctive therapies.

3) Resections should be confined to the stomach and paragastric lymph nodes when the local extent of the cancer permits. This recommendation implies distal gastrectomy with removal of the lesser and greater omenta for cancers in the distal stomach and proximal gastrectomy or total gastrectomy with removal of the omenta for proximal cancers and for those high on the lesser curvature of the stomach.

4) Because it increased morbidity and mortality without appreciably affecting the chances of cure, total gastrectomy with removal of adjacent organs should not be routine unless the primary cancer is in the fundus of the stomach or directly invades the gastrosplenic ligament, the spleen, the distal pancreas or the transverse colon. Cancers of the body or antrum adherent to the pancreas can often be removed from the pancreas, recognizing a risk of pancreatitis. Pancreaticogastroduodenectomy for invasion of the pancreas by cancer should not be performed because it inflicts an unacceptable risk with no greater degree of palliation or likelihood of cure.

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[*] See Moertel, C. G.: Chemotherapy of Gastrointestinal Cancer. N. Engl. J. Med., 299:1049, 1978, for current recommendations.

5) Gastroenterostomies are unsatisfactory palliation. Their use should be limited to patients whose cancer is unresectable and whose major problem is actual or incipient gastric obstruction.

6) Otherwise healthy patients with known residual cancer should be treated with 5-FU in a two-drug or three-drug combination with adriamycin and methyl lomustine or mitomycin C. Although palliation with x-radiation therapy has been disappointing, fast-neutron radiation[12] promises better results.

Acknowledgment

We thank R. Bradford Malt for statistical consultation.

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Management and Survival of Carcinoma of the Colon: Results of a National Survey by the American College of Surgeons

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Survey results of long- and short-term outcome audits of colon cancer in participating hospitals with cancer programs conducted during 1976–7 by the American College of Surgeons are presented. In the long-term audit of 38,621 cases reported by 327 hospitals in 46 states, the overall percentage of cases in localized stage (29.3%) is significantly lower than in the recent series from the National Cancer Institute. The observed survival was substantially lower than the survival rates published in recent smaller series; however, survival approaches the end results for the period 1967–1973. In the short-term audit, the analysis of 11,655 cases diagnosed in 1976 and reported by 491 hospitals from fifty states showed that while 41% of patients had symptoms for less than a month, only 29.5% were diagnosed in the localized stage. Surgery was the predominant treatment modality with an overall resectable rate of 83%. No difference was observed in the stage at diagnosis when the short-term audit (1976) was compared with that found in the long-term audit (1971). The results suggest that the early diagnosis of symptomatic patients may not always substantially improve the cure and survival rate. The screening of asymptomatic patients is suggested as the more promising approach to the substantial improvement of presently less than ideal end results.

From Roswell Park Memorial Institute, Buffalo, New York and the Commission on Cancer—American College of Surgeons

ONE OF THE objectives of the Commission on Cancer—American College of Surgeons is to develop criteria for cancer patient care related to diagnosis, treatment, rehabilitation and follow up.[2] To meet this objective, in 1976, the Committee on Patient Care and Research established a policy for all hospitals with an approved cancer program, that cancer committees conduct regularly evaluative studies of diagnostic procedures, management and end results for selected cancer sites. In order to facilitate this process, the Commission decided to assist cancer committees in approved hospitals to utilize the information accumulated in the registries and medical records and through organizing a national survey to provide the participating hospitals with a national average which would offer a more representative picture of management of cancer patients and end results.

Cancer of the colon has been selected in the study for several reasons. It is the second leading malignancy with 102,000 new cases and 52,000 deaths annually.[1] There is a lack of large representative series with end results. In the evaluation of survival studies based on smaller series, there is always difficulty in interpreting the clinical results, primarily because of the lack of uniform or complete definition of terms. Some clinical assessments utilize as the number of cases the following: a) all patients diagnosed, b) all patients subjected to surgery, c) all patients with resection of primary lesions, and d) all patients treated with resection "for cure." The interpretation of survival figures can be further complicated by the lack of consensus for the reporting of the results of treatment. Operative deaths may or may not be deducted from the survivors in such evaluations. Deaths from causes "other than cancer" may or may not be deducted from such clinical

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Submitted for publication: April 14, 1978.

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TABLE 1. *The Correlation of Classifications as Used in the "Long-term Audit"*

Extent of Disease Classification	Dukes Classification*
Localized—tumor limited to wall of colon	"A" Case—tumor limited to wall of colon
Regional	"B" Case—extension beyond colon to adjacent structures
a) extension to pericolic fat or adjacent organs	"C" Case—extension to regional nodes
b) extension to regional nodes	Distant—spread to distant organs
Distant—spread to distant organs	

* Dukes, C. E., J. Pathol. Bacteriol., 35:323, 1932.

series. This report describes an assessment of the results of this survey.

Methods

In December 1976, the cancer committees in each of the 742 hospitals with an approved cancer program were invited to voluntary participation in long-term and short-term audit of colon cancer patient care. Detailed audit formats with specific instructions were prepared and forwarded to all hospital committee chairmen.

A. Long-term Audit

The objective of this part of the project was to obtain information on absolute five years survival of colon cancer patients and to evaluate the quality of follow-up. All participating hospitals were asked to report on 100 consecutive patients who received definitive treatment before December 31, 1971. The study was designed to include all histologically confirmed cases regardless of treatment. Specific instructions were given to exclude carcinoma *in situ* in polyps or carcinoma of the rectum. The anatomical limits of the rectum were defined as extending 15 cm proximal to the anal orifice. The categories used for clinical staging of the primary tumor were either localized, regional or distant. The correlation of the extent of disease with Dukes' original classification is shown in Table 1.

B. Short-term Audit

The short-term evaluation included patients with histologically confirmed cancer of the colon admitted during 1976 who had no prior definitive treatment for this cancer. Patients with carcinoma *in situ* or carcinoma in a pedunculated polyp or carcinoma of the rectum were not included in this study. Hospitals with more than 25 admissions were instructed to include at least 25 consecutive admissions, while hospitals admitting fewer than 25 patients were to include all cases.

Specific questions were asked concerning duration of symptoms prior to admission, reasons for hospitalization, pretreatment examinations, staging, treatment modalities, complications and length of hospitalization. The purpose of this study was to obtain a general picture on a larger scale of the present state of diagnostic and therapeutic approaches in the care of this malignancy, and to ascertain changes, if any, in the trend of staging over the five year period.

Results

A. Long-term Audit

As a result of national voluntary participation there were 38,621 cases reported by 327 hospitals in 46 states. California, New York and Pennsylvania each accounted for over 4,000 cases. The percentage of cases lost to follow-up during the five year period was less than 10%, with some hospitals reporting almost 100% follow-up.

The distribution of cases by part of the colon did not differ substantially from other series.[3,8] Twenty-nine per cent of tumors occurred in ascending colon, 16% in transverse colon, 9% in descending colon, 44% in sigmoid colon and 2% of cases were reported as multiple sites.

TABLE 2. *The Anatomic Distribution of Colon Cancer as Observed in the "Long-term Audit" Portion of the National Study by Stage*

	Localized		Regional		Distant		All Stages	
Part of Colon	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
Ascending	3057	27.7	5958	53.9	2032	18.4	11,047	100
Transverse	1755	28.1	3206	51.4	1279	20.5	6240	100
Descending	1012	30.3	1738	52.1	589	17.6	3339	100
Sigmoid	5254	30.7	8257	48.2	3627	21.2	17,138	100
Multiple sites	253	29.5	348	40.6	256	29.9	857	100
Colon Total	11,331	29.3	19,507	50.5	7783	20.2	38,621	100

TABLE 3. *The Five Year Absolute Survival by Anatomic Distribution and by Stage of Cases of Colon Cancer as Observed in the "Long-term Audit" Portion of the National Survey*

	Localized		Regional		Distant		All Stages	
Part of Colon	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
Ascending	3057	57.4	5958	36.5	2032	2.9	11,047	36.
Transverse	1755	56.6	3206	36.6	1279	2.7	6240	35.
Descending	1012	57.1	1738	41.4	589	3.9	3339	39.
Sigmoid	5254	57.8	8257	36.6	3627	3.2	17,138	35.
Miltiple sites	253	54.6	348	35.1	256	17.2	857	35.
Colon Total	11,331	57.2	19,507	36.6	7783	3.5	38,621	36.

The detailed distribution by segment of colon and by stage of disease is shown on Table 2. Again, the lowest percentage of cases with tumor in the ascending colon in localized stage (27.7%) and the highest per cent of localized tumors found in sigmoid colon (30.7%) is not surprising and corresponds with other series.[3,8] However, the overall proportion of cases in localized stage for the whole colon (29.3%) is significantly lower than in the end results series[3] in which 40% of cases were classified as localized.

Table 3 displays the absolute five year survival rate for tumors of the colon by segment of the colon and by stage. All individuals found living (living free of cancer, living with cancer and living cancer status unknown) at the end of five years after diagnosis were included in the survival rates calculations. Detailed breakdown of survivors by cancer status revealed that 82% of cases were free of cancer, 8% were living with cancer while in 10% of cases cancer status was unknown.

B. Short-term Audit

There were 11,655 cases reported by 491 hospitals from 50 states, Washington, D.C. and Puerto Rico. The duration of symptoms prior to admission was less than one month in 41% of the cases, whereas only 15% of the patients were symptomatic more than six months. The frequency of various reasons for hospitalization is summarized in Table 4, which shows that abdominal pain and bleeding from lower gastrointestinal tract were the most frequent. It is worth noting that in almost one-fifth of the cases the diagnosis was made prior to admission. This sould be born in mind when interpreting Table 5, which summarizes the pattern of pretreatment examinations. Nevertheless, these responses indicate that of the routine pretreatment examinations suggested by the American College of Surgeons,[6] there were two frequent omissions: only 58% of the patients had proctosigmoidoscopy and only 44% of the patients had occult blood exams. The information regarding other selected pretreatment examinations is summarized in Table 6. It is of interest that intravenous pyelogram was performed in only 35% of the cases while more than 50% of tumors might occur near ureters by definition of site of occurrence. Colonoscopy is apparently not in widespread use in some areas as yet. Carcinoembryonic antigen would appear to have been adopted by the surgical community with nearly one-third of the patients receiving the test.

As in other series, surgery has been the predominant method of treatment. As shown in Table 7, surgical resection for cure was performed in 68.5% of cases; another 14.5% had palliative resection for a resectable rate of over 83%. This is comparable to previous re-

TABLE 4. *Stated Reasons for Hospitalization for Treatment of Colon Cancer*

	Number of Cases	% of All 11,655 Cases
Diagnosis of colon cancer prior to admission	2266	19.4
Bleeding from lower GI	3448	29.6
Intra-abdominal mass	1665	14.3
Unexplained diarrhea	1891	16.2
Obstruction of colon	1333	11.4
Unexplained anemia	2075	17.8
Abdominal pain	5459	46.8
Constipation	2362	20.3
Unrelated to cancer	1354	11.6

TABLE 5. *Pretreatment Examinations Performed on Patients with Colon Cancer*

	Number of Cases	% of All 11,655 Cases
Complete history and physical exam	11,201	96.1
Proctosigmoidoscopy	6756	58.0
Chest x-ray	10,962	94.0
Complete blood count	11,402	97.8
Blood chemistry	11,109	95.3
Digital rectal exam	9496	81.5
Barium enema (regular)	9800	84.1
Electrocardiogram	10,618	91.1
Urine exam	11,131	95.5
Stool exam	5187	44.5

TABLE 6. *Special Pretreatment Examinations Performed on Patients with Colon Cancer*

	Number of Cases	% of All 11,655 Cases
Intravenous pyelogram	4175	35.8
Fiberoptic colonoscopy	1409	12.1
Liver scan	4902	42.1
Carcinoembryonic antigen	3557	30.5
Contrast barium enema	1585	13.6
Sonogram	455	3.9

ports in the literature.[5] Surgery combined with chemotherapy was the most frequent treatment modality reported, (15.2%) followed by chemotherapy alone (2.2%) and surgery and radiation (1.7%). Immunotherapy alone, radiation alone and other combinations were each used in less than 1% of patients.

The complications and mortality of this series of patients is detailed in Table 8, and reveals that despite seventy-five years of surgical experience in colorectal surgery, the mortality and morbidity are still quite significant. This is most probably related to the age and general status of these patients, as documented by frequent occurrence of cardiovascular and pulmonary complications.

Thirty per cent of patients were discharged in less than 14 days, while 17% of patients were hospitalized for more than thirty days. Interestingly, detailed analysis of length of stay revealed that, in general, length of hospitalization is shorter in smaller hospitals with less than 200 beds. This finding was not related to the stage of disease.

The distribution of cases by stage of disease is summarized in Table 9. It shows, when compared with Table 2, that between the years 1971 and 1976, there was no change in the proportion of localized cases at the time of diagnosis.

TABLE 7. *The Type of Primary Surgical Treatment Performed in Reported Cases of Colon Cancer*

	Number of Cases		% of All 11,655 Cases	
1. Exploratory procedure	286		2.4	
2. Curative resection				
A. One stage	6,600	7,989	56.6	68.6%
B. Two stage	963		8.3	
C. Three stage	426		3.7	
3. Palliative procedure				
A. Bypass	158	2,415	1.3	20.7%
B. Colostomy only	566		4.9	
C. Palliative resection	1,691		14.5	
4. No surgery	649		5.6	
5. Type of surgery not specified	316		2.7	
Total	11,655		100.0	

TABLE 8. *Reported Complications and Mortality in Operative Cases of Colon Cancer*

	Number of Cases	% of All 11,655 Cases
Death following surgery	765	6.6
Death—no surgery	241	2.1
Wound infection	812	7.0
Anastomatic leak	134	1.1
Wound dehiscence	176	1.5
Fistula	232	2.0
Intestinal obstruction	458	3.9
Intra-abdominal abscess	313	2.7
Urinary tract infection	582	5.0
Pulmonary complications	916	7.8
Cardiac complications	954	8.2
Cerebrovascular complications	159	1.4
Phlebothrombosis	140	1.2
Intra-abdominal hemorrhage	100	0.9

Discussion

The remarkable response and completeness of the data provided in a relatively short time-period is a tribute to the cancer committees and tumor registrars in all participating hospitals. The data presented in this report seem to reflect more realistically the present situation in diagnosis, treatment and end results of colon cancer. Despite the possible variation between so many hospitals, both series are large enough to be considered of value for future comparisons.

The classification system used (localized, regional and distant) is well known to most registrars and has been consistently used for end results reporting.[3,8]

In view of these factors, the findings of only 29.3% of cases in localized stage is surprising and in a strong contrast with the 40% localized cases reported in end results series.[3] However, the overall percentage of cases classified as distant is lower than reported by others.[3,8] These differences indicate that more than 70% of colonic tumors are diagnosed as rather advanced lesions and to a great extent explain the less than optimal survival results. It should be born in mind,

TABLE 9. *The Stage of Colon Cancer Cases Surveyed in the "Short-term Audit"*

	Number of Cases		% of All 11,655 Cases	
Localized	3,434		29.5	
Regional				
A. To pericolic fat or adjacent tissue	2,496	5,557	21.4	47.7%
B. To regional lymph nodes	1,295		11.1	
C. To both A and B	1,766		15.2	
Distant	2,506		21.5	
Stage not known	158		1.3	
All stages	11,655		100.0	

however, that survival rates for localized as well as regional lesions in this series were also substantially lower than in series reported previously;[3,8] however, they do correspond with end results series for the period of 1967–1973. It would seem that the generally accepted concept that a surgical procedure always offers a significant benefit to patients with localized disease is not necessarily supported by the results of this survey.

Another finding of interest is a relatively large proportion of patients with less than a month duration of symptoms (41%) when compared with proportion of cases with localized lesions (29.3%). It would seem less certain that the early diagnosis of symptomatic patients will result in a significant increase of cure and survival rates. These results are in agreement with those of Copeland[4] and Slaney[7] who were unable to find any evidence of improved survival in patients with carcinoma of the colon presenting with a short history of symptoms. Under these circumstances, the screening of asymptomatic population at high risk of developing the disease seems at present the most promising solution.

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In search of the ideal analgesic

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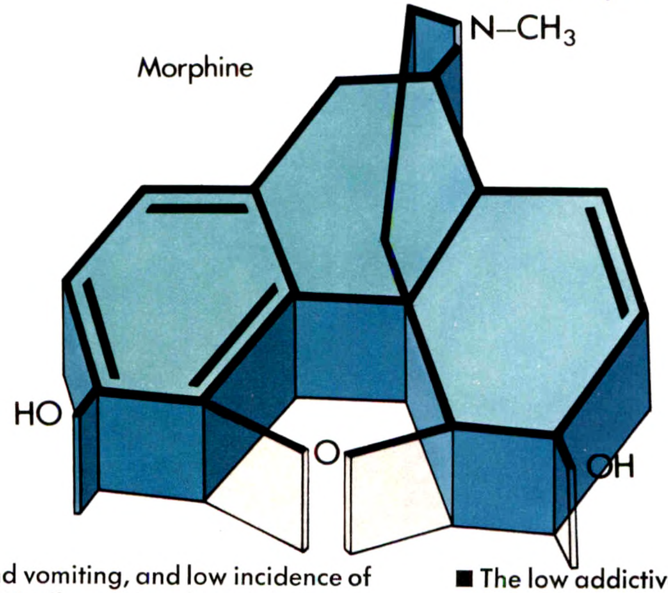
■ Distinguished by its favorable side effects profile,[1-16, 31-33, 36, 37]—low physical-dependence liability, limited respiratory depressant effect, little nausea and vomiting, and low incidence of CNS effects other than sedation.

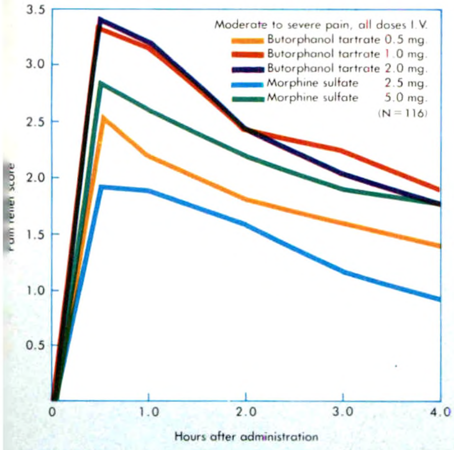


■ 2 mg. of Stadol produces an order of respiratory depression similar to that caused by 10 mg. of morphine. In contrast to morphine, increasing Stadol doses yield greater analgesic effect,[9] without appreciably increasing liability for respiratory depression.[16]

■ The low addictive potential of Stadol[24] is underscored by its narcotic antagonist properties.

Stadol is not recommended for patients physically dependent on narcotics or with significant previous narcotic experience. Its use in such patients, without prior detoxification, will result in induction of withdrawal reactions.

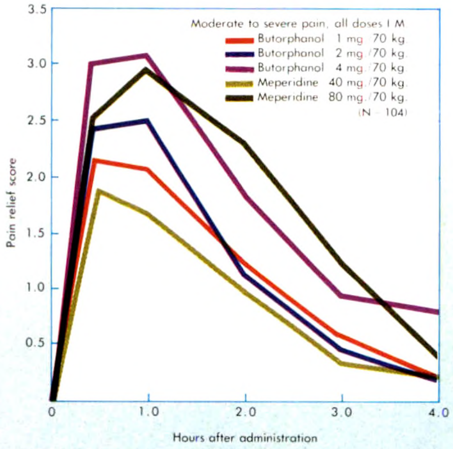
Unsurpassed pain relief



Average mean pain relief scores
In response to butorphanol tartrate and morphine sulfate

In this study "... butorphanol tartrate 0.5 mg produced greater relief than morphine sulfate 2.5 mg and butorphanol tartrate 1.0 and 2.0 mg produced greater relief than morphine sulfate 5.0 mg." **(DelPizzo[1])**

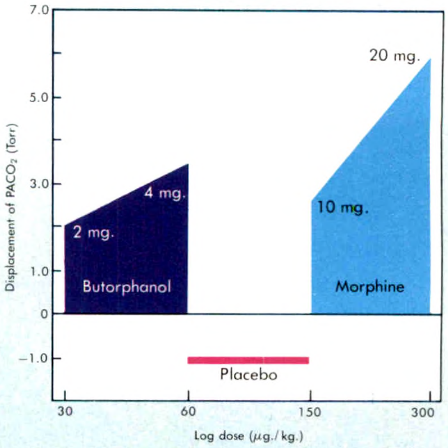
Unsurpassed pain relief



Average mean pain relief scores
In response to butorphanol tartrate and meperidine hydrochloride

In moderate to severe pain, butorphanol tartrate provided relief "... that was not statistically distinguishable from that achieved with 80 mg/70 kg meperidine." **(Gilbert et al[5])**

Limited respiratory depressant effect

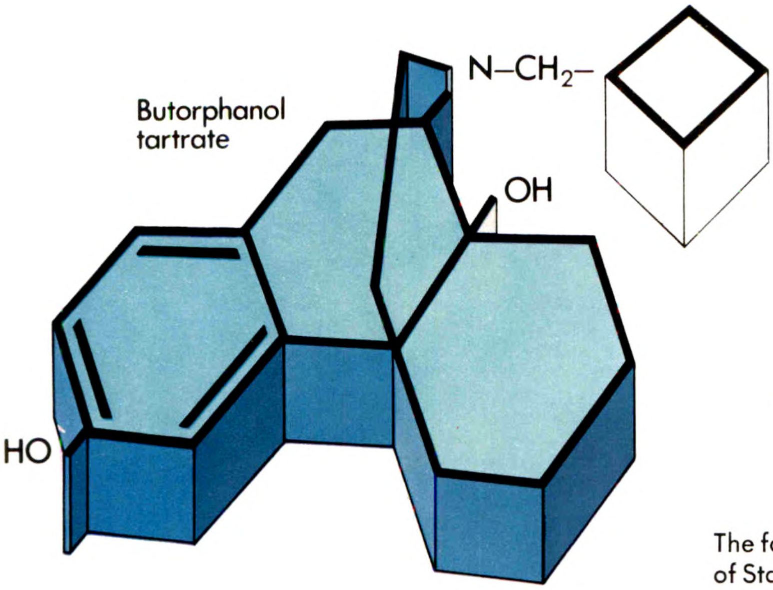


Log dose $PACO_2$ displacement curves

In this graph based on alveolar carbon dioxide tension ($PACO_2$) measurements, the flatter the curve, the less respiratory depression. "The flat dose-response curve ... of butorphanol may indicate that, because of its antagonistic properties, there is a limit to its respiratory depressant effects. **(Adapted from Nagashima et al[16])** **Unlike morphine with its steep dose-response curve, the magnitude of respiratory depression does not increase in a dose-related manner with Stadol, within the range of recommended doses.**

Please see last page for a brief summary of prescribing information.

closer to the ideal parenteral analgesi



new Stadol® IM IV

(butorphanol tartrate)

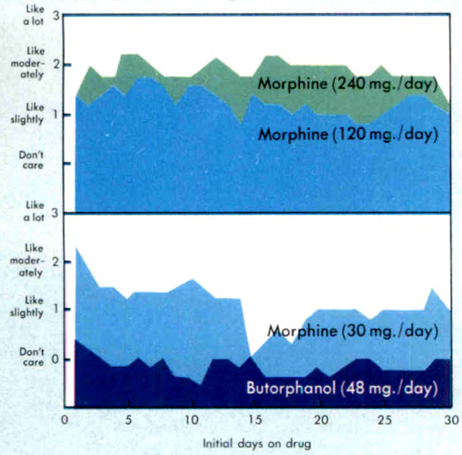
another step closer to the ideal

The following table shows a side-by-side clinical compariso of Stadol with both morphine and meperidine.

Clinical parameters	Meperidine	Morphine	Stadol
Classification	narcotic	narcotic	**nonnarcotic**
Indication	moderate to severe pain	moderate to severe pain	**moderate to severe pain**
Standard I.M. dose	75–100 mg.	8–10 mg.	**2 mg. (1 to 4 mg.)**
Standard I.V. dose	50–100 mg.	4–10 mg.	**1 mg. (0.5 to 2 mg.)**
Usual route of administration	I.M./I.V.	I.M./I.V.	**I.M./I.V.**
Onset of pain relief	30 minutes I.M., very rapidly I.V.	30 minutes I.M., very rapidly I.V.	**less than 30 minutes I.M., very rapidly I.V**
Peak analgesic activity	within 1 hour I.M., within 30 minutes I.V.	within 1 hour I.M., within 20 minutes I.V.	**within 1 hour I.M., within 30 minutes I.V.**
Duration of pain relief I.M./I.V.	slightly less than morphine	about 4 hours	**3–4 hours**
Addicting potential	high	high	**low**
Respiratory effects	dose-related depression	dose-related depression	**limited depression—no appreciable dose-related increase within the rang of recommende doses.**

Data for this table were obtained from: Jaffe, J. H. and Martin, W. R.: Narcotic analgesics and antagonists, in The Pharmacological Basis of Therapeutics (Goodman, L. S. and Gilman, A., eds.), ed. 5, New York, Macmillan, 1975, pp. 245–283; AMA Drug Evaluations, ed. 3, Chicago, 1977, pp. 325–339; and from manufacturer recommendations.

Low physical-dependence liability



Preference scores completed by subjects during chronic butorphanol tartrate administration compared with scores from three other groups of subjects receiving 30, 120 and 240 mg. of morphine daily. (Adapted from Jasinski et al[24])

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INDICATIONS AND USAGE— (1) 8/18/78

Stadol is recommended for the relief of moderate to severe pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients physically dependent on narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical-dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head injury and increased intracranial pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular effects: Because Stadol increases the work of the heart, especially the pulmonary circuit (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain respiratory conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired renal or hepatic function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage in pregnancy: The safety of Stadol for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in labor and delivery: Safety to the mother and fetus following administration of Stadol during labor and delivery has not been established.

Usage in nursing mothers: The use of Stadol is not recommended in nursing mothers since it is not known whether this drug is excreted in human milk.

Pediatric use: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS effects: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic effects: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors, and assisted or controlled respiration.

DOSAGE AND ADMINISTRATION—*Adults:* Intramuscular—The usual recommended single dose is 2 mg. This may be repeated every three to four hours, as necessary. The effective dosage range, depending on the severity of pain, is 1 to 4 mg. repeated every three to four hours. At this time, there is insufficient clinical data to recommend single doses beyond 4 mg.

Intravenous—The usual recommended single dose for intravenous administration is 1 mg. repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg. repeated every three to four hours.

Children: Since there is no clinical experience in children under 18 years, Stadol is not recommended in this age group.

Storage conditions: When stored at room temperature, the stability of the solution in vials is 2 years.

SUPPLY—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, 2 mg. per ml., 2-ml. vial; 1 mg. per ml., 1-ml. vial; 2 mg. per ml., 1-ml. vial; 2 mg. per ml., 10-ml. multi-dose vial.

NDC 0015-5644–2 mg. per ml., 2-ml. vials
NDC 0015-5645–1 mg. per ml., 1-ml. vials
NDC 0015-5646–2 mg. per ml., 1-ml. vials
NDC 0015-5648–2 mg. per ml., 10-ml. multi-dose vials

For information on package sizes available, refer to the current price schedule.

BRISTOL™

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Div. of Bristol-Myers Company
Syracuse, New York 13201

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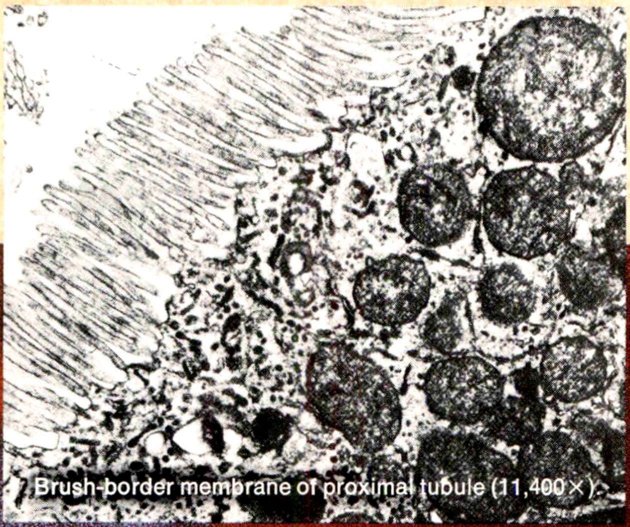
Selecting an aminoglycoside:

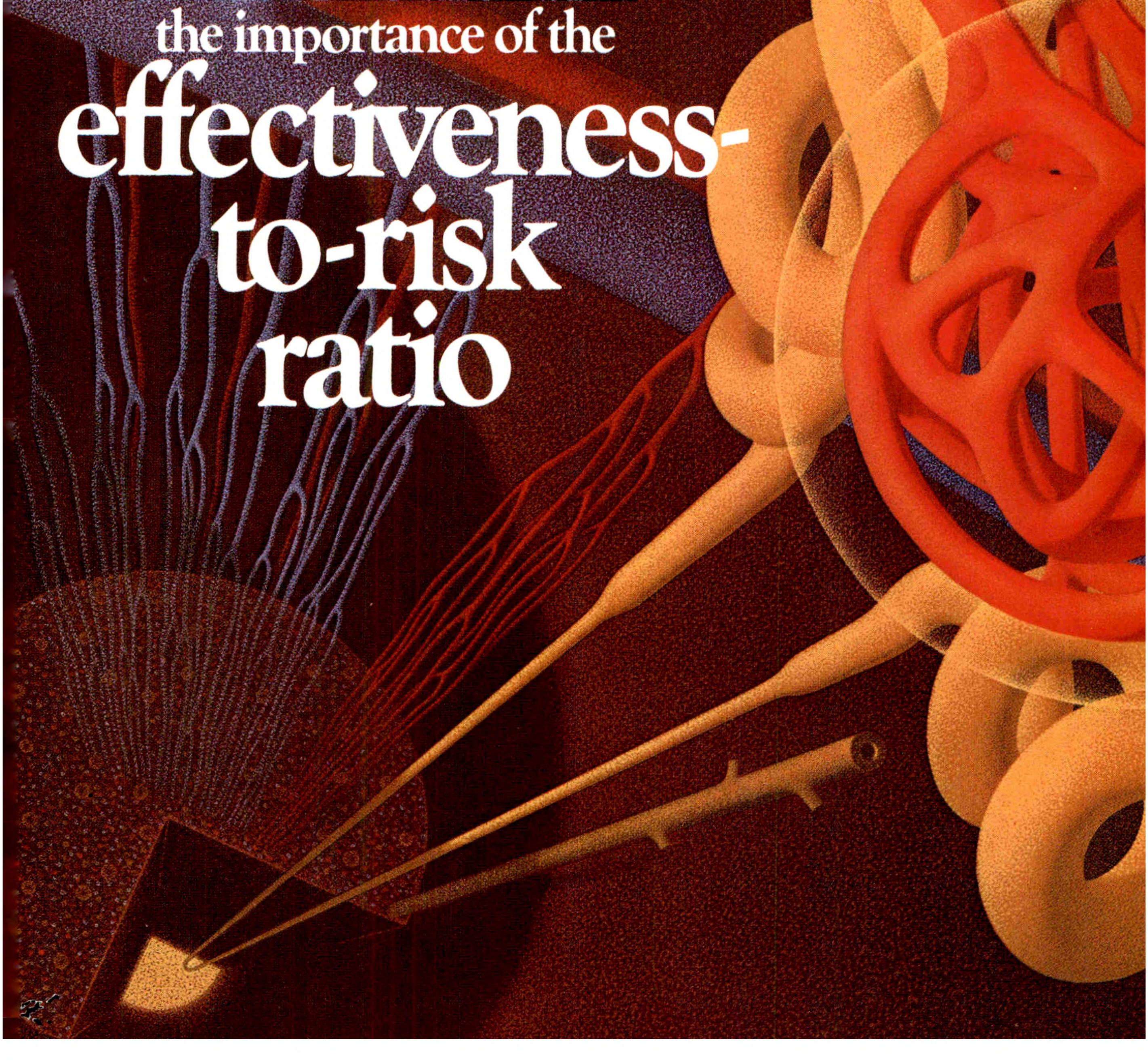
In patients with serious bacterial infection, the choice of antibiotic therapy is usually made on the basis of the effectiveness-to-risk ratio. This consideration is particularly important when an aminoglycosid antibiotic is indicated.

The activity of Nebcin® (tobramycin sulfate, Lilly) against a wide range of gram-negative organisms is now well known. A review of worldwide literature shows "that tobramycin has significant antibacterial activity and that it is the most potent of all aminoglycosides against *P. aeruginosa.* The antibacterial



Brush-border membrane of proximal tubule (11,400×).

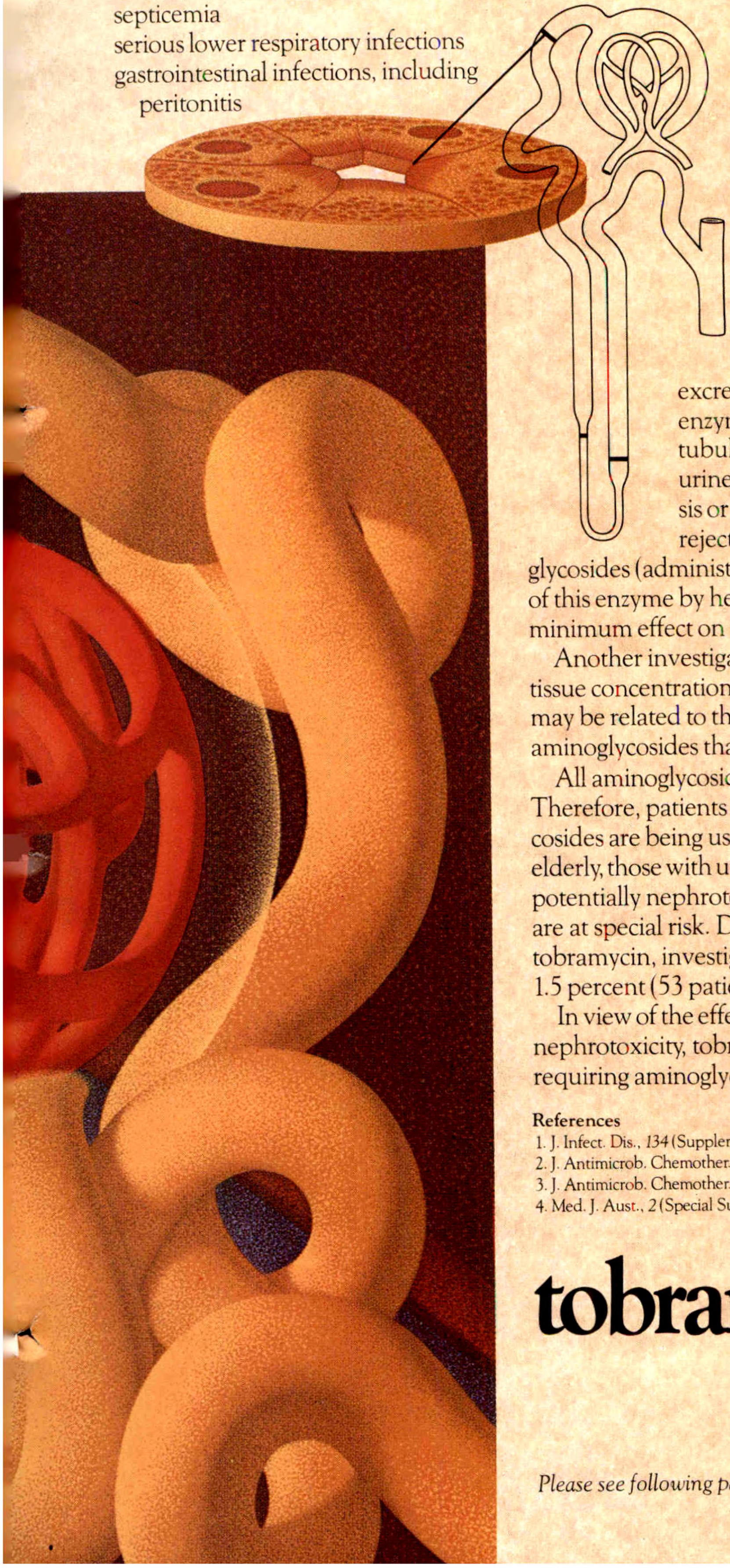
the importance of the effectiveness-to-risk ratio



activities of tobramycin and gentamicin against members of the Enterobacteriaceae are comparable, with each agent possessing slightly greater activity than the other against selected strains of any species."[1]

Nebcin is indicated in the treatment of
- septicemia
- serious lower respiratory infections
- gastrointestinal infections, including peritonitis
- serious complicated and recurrent urinary tract infections
- serious skin, bone, and soft-tissue infections, including burns

caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).



The proximal tubule

The proximal tubule is the site in the renal system where aminoglycosides produce nephrotoxicity.

An investigator has studied the urinary excretion of alanine aminopeptidase, a principal enzyme of the brush-border membrane of the proximal tubule.[2] Levels of the enzyme become elevated in the urine as a result of toxic lesions in acute tubular necrosis or of inflammatory processes in the kidney, such as rejection crisis. In measurements of the effect of aminoglycosides (administered for three consecutive days) on the excretion of this enzyme by healthy humans, tobramycin appeared to have a minimum effect on the brush-border membrane.

Another investigative team has studied the relationship between tissue concentration and toxicity.[3] The toxicity of aminoglycosides may be related to the degree of their binding to tissue. Hence, aminoglycosides that accumulate less may be less nephrotoxic.

All aminoglycosides are potentially nephrotoxic and ototoxic. Therefore, patients should be monitored closely when aminoglycosides are being used. Patients with impaired renal function, the elderly, those with underlying disease, those with prior exposure to potentially nephrotoxic agents, and those with poor host resistance are at special risk. During clinical trials in 3506 patients treated with tobramycin, investigators reported drug-related nephrotoxicity in 1.5 percent (53 patients).[4]

In view of the effectiveness of Nebcin and the relatively low risk of nephrotoxicity, tobramycin can be an appropriate choice for patients requiring aminoglycoside therapy.

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tobramycin/Nebcin ◆I.M./I.V

tobramycin sulfate

80 mg* in 2-ml ampoules

*Equivalent to tobramycin.

Please see following page for a brief summary of the prescribing information.

800730

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Nebcin® ◆ I.M./I.V.
tobramycin sulfate

Summary of Prescribing Information

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: *See* WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility that prolonged or secondary apnea may occur should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

The usual duration of treatment is seven to ten days.

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg/kg/day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg/kg/day administered in three or four equal doses. This dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg/kg/day may be given in two equal doses every 12 hours.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg/kg, subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.* To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg/kg q (6 × serum creatinine) h

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of 20 to 60 minutes.

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*An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function (Dosage at Eight-Hour Intervals)

For Patient Weighing kg	lb	Usual Dose for Serious Infections 1 mg/kg q 8 h (Total, 3 mg/kg/day) mg/dose q 8 h	ml/dose†	Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg/kg q 8 h (Total, 5 mg/kg/day) mg/dose q 8 h	ml/dose†
120	264	120 mg	3 ml	200 mg	5 ml
115	253	115 mg	2.9 ml	191 mg	4.75 ml
110	242	110 mg	2.75 ml	183 mg	4.5 ml
105	231	105 mg	2.6 ml	175 mg	4.4 ml
100	220	100 mg	2.5 ml	166 mg	4.2 ml
95	209	95 mg	2.4 ml	158 mg	4 ml
90	198	90 mg	2.25 ml	150 mg	3.75 ml
85	187	85 mg	2.1 ml	141 mg	3.5 ml
80	176	80 mg	2 ml	133 mg	3.3 ml
75	165	75 mg	1.9 ml	125 mg	3.1 ml
70	154	70 mg	1.75 ml	116 mg	2.9 ml
65	143	65 mg	1.6 ml	108 mg	2.7 ml
60	132	60 mg	1.5 ml	100 mg	2.5 ml
55	121	55 mg	1.4 ml	91 mg	2.25 ml
50	110	50 mg	1.25 ml	83 mg	2.1 ml
45	99	45 mg	1.1 ml	75 mg	1.9 ml
40	88	40 mg	1 ml	66 mg	1.6 ml

†Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules (Vials) Nebcin® (tobramycin sulfate, Lilly), Injection, 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1 and Traypaks™ (multivial cartons, Lilly) of 25.

Ampoules (Vials) Nebcin, Pediatric, Injection, 20 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1.

Hyporets® (disposable syringes, Lilly) Nebcin, Injection, 60 mg (equivalent to tobramycin) per 1.5 ml, 1.5 ml, and 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, in packages of 24.

Each ml also contains 5 mg phenol as a preservative, 3.2 mg sodium bisulfite, 0.1 mg edetate disodium, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [030476C]

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46206.

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Each 10 cc. ampul† or 5 cc. Concentrate vial†† provides:

Ascorbic acid (C)	500 mg.
Vitamin A*	10,000 I.U.
Vitamin D* (ergocalciferol)	1,000 I.U.
Thiamine HCl (B_1)	50 mg.
Riboflavin (B_2)**	10 mg.
Pyridoxine HCl (B_6)	15 mg.
Niacinamide	100 mg.
Dexpanthenol	25 mg.
Vitamin E* (dl-alpha tocopheryl acetate)	5 I.U.

†With sorethytan laurate 1%, sodium hydroxide 1%, butylated hydroxytoluene 0.003%, butylated hydroxyanisole 0.0008%; and gentisic acid ethanolamide 2% as preservative.

††With propylene glycol 30% and gentisic acid ethanolamide 2% as stabilizers and preservatives, sodium hydroxide for pH adjustment, sorethytan laurate 1.6%, butylated hydroxytoluene 0.006%, butylated hydroxyanisole 0.0015%.

*Oil-soluble vitamins A, D and E water solubilized with sorethytan laurate.

**In Concentrate as riboflavin-5-phosphate.

PRODUCT INFORMATION

INDICATIONS: *in emergency feedings* – Surgery, extensive burns, fractures and other trauma, severe infectious diseases, comatose states, etc. may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. As a result, wound healing may be impaired, enzyme activity disturbed, hematopoietic tissues affected; hypoproteinemia and edema may appear; convalescence is thus prolonged.

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For intravenous feeding, one daily dose of 10 cc. of M.V.I. or 5 cc. of M.V.I. Concentrate added directly to not less than 500 cc., preferably 1,000 cc., of intravenous dextrose, saline or similar infusion solutions... plasma, protein hydrolysates, etc.

PRECAUTION: Allergic reaction has been known to occur following intravenous administration of solutions containing thiamine.

CAUTION: Not to be given as a direct undiluted intravenous injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be discontinued as early as practical in favor of an intramuscular or oral vitamin preparation, if deemed advisable.

HOW SUPPLIED: M.V.I.—10 cc. ampuls, boxes of 25 and 100 (NSN 6505-00-455-9955/NSN 6505-00-424-9808A).

M.V.I. CONCENTRATE—5 cc. vials, boxes of 25. Available in 100s only (NSN 6505-00-212-6156A).

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Better patient compliance **2** The specific instructions accompanying a prescription may encourage patients to adhere to the regimen *you* recommend.

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Each Berocca Tablet contains:

Thiamine mononitrate (Vitamin B_1)	15 mg
Riboflavin (Vitamin B_2)	15 mg
Pyridoxine HCl (Vitamin B_6)	5 mg
Niacinamide	100 mg
Calcium pantothenate	20 mg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Folic acid	0.5 mg
Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

Dosage: 1 or 2 tablets daily, as indicated by clinical need.

Available: In bottles of 100 and 500.

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The Surgical Management of Acute Occlusion of the Superior Mesenteric Artery

LESLIE W. OTTINGER, M.D.

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A study of 103 cases of acute occlusion of the superior mesenteric artery is presented. The relation of site of occlusion to etiology, extent of infarction, and survival following resection and revascularization is described. Included is an analysis of the technical factors contributing to successful revascularization, the specific complications of revascularization, and the application of elective second look operations and angiographic techniques. The persistent high mortality (85% in this series) can probably be reduced but only by advances in these areas along with progress in the more general aspects of management of elderly patients with multiple system problems and failure.

ACUTE OCCLUSION of the superior mesenteric artery (SMA) or its major branches is found to be the cause in about 40% of the patients who are admitted with or who develop mesenteric infarction in our hospital.[6] Before the 1950's, resection alone was the only useful means of management. During that decade, the development and wide application of techniques for restoring arterial flow promised to alter the previously high mortality for this group of patients. Revascularization with or without resection has subsequently been widely employed by abdominal and vascular surgeons.

The first attempts at embolectomy for mesenteric infarction were described by Klass.[5] Stewart and associates accomplished the first embolectomy with survival in 1951.[9] In 1957, Shaw and Rutledge published the most important early paper on embolectomy of the SMA, describing a case with survival but more importantly, also outlining the principles of management of such cases so fully that little has been added to them in the succeeding two decades.[8] In 1958, Shaw also published the first case of successful thromboendarterectomy for acute thrombosis of the SMA.[7]

Despite these early successes, the management of patients with mesenteric infarction has remained a frustrating problem characterized by a persistently high mortality. The fact that reports of individual or a few cases managed successfully continue to appear is testimony that the desired progress in overall management has eluded surgeons. The analysis reported in this paper was undertaken to discover those elements of technique that contribute to the continued poor prognosis of patients with acute occlusion of the mesenteric artery.

Patient Material

The records of 103 patients who had intestinal ischemia or infarction resulting from acute occlusion of the SMA or one of its branches and were managed on the surgical services of the Massachusetts General Hospital between 1964 and 1975 were reviewed. This paper summarizes the findings and conclusions. The diagnoses were proved by angiography, laparotomy, or postmortem examination. Excluded were patients whose infarction was an unexpected finding at autopsy and those in whom it was the result of venous thrombosis, arteritis, aortic dissection, or in whom it had occurred in the absence of demonstrable acute major vascular occlusion. Nine patients included in the series did not undergo abdominal operations, but in these, the diagnosis was confirmed by angiography or by postmortem examination.

Of the 103 patients, 57 (55%) had emboli and 46 (45%) had severe atherosclerotic narrowing with superimposed acute thrombosis. In a few, of course, certainty as to the etiology was not possible and assignment to one or the other group was made on the basis of local findings, the impression of the surgeon, and the presence of absence of other emboli. As shown in Table 1, there were more women than men in both groups, especially in those with thrombosis. The median age was 70 years. Figure 1 shows the distribution in both groups by decades. The peak for patients with

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Submitted for publication: April 24, 1978.

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TABLE 1. *Diagnosis as it Relates to Sex*

	Men	Women	Total
Emboli	25	32	57
Thrombi	13	33	46
Total	38	65	103

emboli was the seventh decade and for those with thrombosis, the eighth. The mortality was 85%; only 15 patients survived to be discharged from the hospital. For emboli, the mortality was 77% and for thrombi, 96%. Sixty-five deaths could be attributed directly to the mesenteric infarction. The other 23 patients died of remotely related complications or unrelated medical problems. Had infarction been the only diagnosis, several of these patients would have survived.

Twenty-two patients had had an operation during the same hospitalization but before the onset of symptoms of mesenteric occlusion. In five, these were either vascular or cardiac procedures and were causally related to the superior mesenteric artery embolus. In seven others, the preceding operation was for another embolus. Only a coincidental relationship was apparent in the other ten.

Anatomic Considerations

The SMA normally serves as the primary arterial supply of the jejunum, ileum, and colon to the level of the splenic flexure. Its major branches are connected by peripheral anastomatic arcades. The most peripheral of these is designated the marginal artery and gives origin to the vasa recti. The marginal arteries of the SMA are continuous with those of the celiac axis (CA) and the inferior mesenteric artery (IMA). In the presence of gradual occlusion of the origin of the SMA or that of its branches, the arcades from adjacent vessels can adequately supply the deprived areas. With acute occlusion, however, they are usually not adequate and then infarction of all or at least the central portion of the intestine directly dependent on the occluded vessel ensues. Previous chronic occlusion of the CA or IMA, arterial spasm, and diminished central perfusion pressure may all influence the adequacy of the collateral supply and thereby the extent of the infarction. Although anomalies of the mesenteric arterial circulation are common, they were shown to have no role in the cases reviewed in this paper.

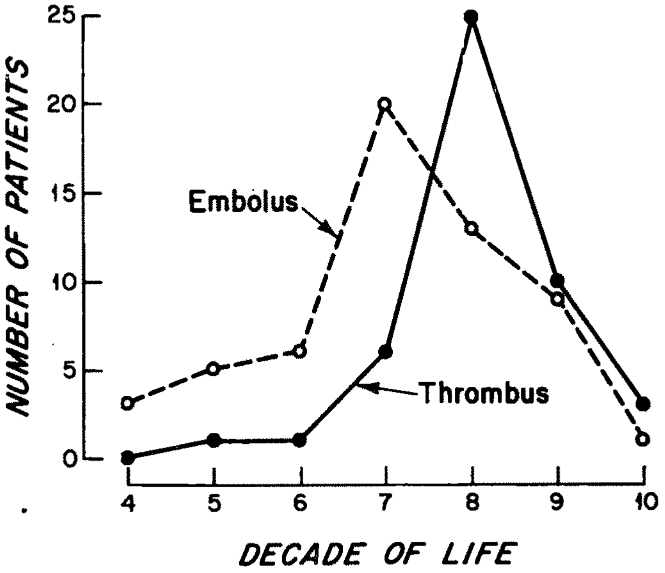

FIG. 1. Distribution by decade of life of patient with embolic and thrombotic occlusion of the superior mesenteric artery.

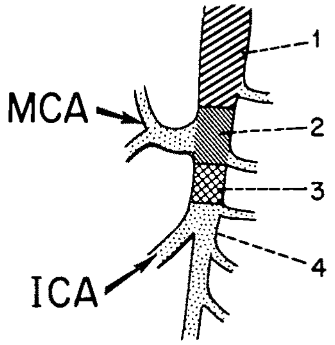

FIG. 2. Regions of the superior mesenteric artery. MCA is the middle colic artery; ICA, the ileocolic artery.

Occlusion of the SMA at its origin should result in more extensive infarction than when the site of the occlusion is distal to the origin of some of its branches. To test this premise, the site of occlusion was compared to the length and location of the affected intestine. The SMA was divided into regions (Fig. 2). *Region 1* is the origin; *region 2*, the main trunk including the origin of the middle colic artery (MCA); *region 3*, the main trunk beyond the origin of the MCA; and *region 4*, the more peripheral portion of the SMA and its branches. Both the site of occlusion and the extent of infarction could be accurately determined in 100 patients, and Table 2 presents the data from this analysis. It demonstrates a general correspondence between site and extent. The lack of complete correlation presumably reflects variability in collateral flow.

The origin of the SMA is the region most commonly involved by atherosclerotic narrowing. Since thrombosis is usually a complication of such narrowing, it is logical to expect region 1 to be the usual site of thrombosis. Conversely, arterial emboli generally lodge at a site of normal anatomic narrowing, usually the origin of a major branch. Table 3 relates site to diagnosis and confirms that these general rules apply to SMA occlusion. It also shows the region of occlusion for survivors in both groups. Finally, it can be predicted that infarction resulting from SMA thrombosis will generally be more extensive than that resulting from emboli. Table 4 shows that this was true in this series.

Clinical Presentation

The symptom of abdominal pain lends uniformity to the clinical presentation of intestinal infarction. It was reported by all patients in this series for whom a history was recorded. Thus, in the absence of pain, the diagnosis of mesenteric ischemia or infarction may be discarded. The nature and location of the pain, however, was found to be variable. Though it was usually steady and severe, this was not always true. It was generally referred to the anterior midportion of the abdomen but was sometimes felt in the epigastric or suprapubic areas. Duration of pain prior to the time the diagnosis was suspected varied, ranging from a few hours to 14 days. Duration could not be related to reversability of the intestinal injury with revascularization in this series. Neither long duration nor delay in diagnosis worsened the prognosis, indicating that survival was primarily dependent on other factors. In addition to pain, the history included vomiting in 56% of the patients and diarrhea in 29%. Previous peripheral emboli had been documented in eight of the 57 patients with embolic occlusion, and this history was of some help in suggesting the diagnosis in them. Many patients had coronary or peripheral vascular occlusive disease, but considering the average age of the patients, this observation was neither surprising nor useful.

Occult blood either in the gastric or the rectal contents or in both was present in 25% of the patients. In the physical examination, no other findings were revealed to suggest mesenteric occlusion except in patients in whom infarction and associated peritonitis were far advanced.

For diagnostic purposes, laboratory tests also were of limited value. In 59 patients, a white blood count was available. It was less than 10,000/mm³ in six (10%); 10,000 to 20,000/mm³ in 27 (46%); and greater than 20,000/mm³ in 26 of the patients (44%). The degree of elevation was somewhat related to the extent of infarction and duration of symptoms. Serum amylase was recorded in 35 patients. It was elevated in 17 (50%), but in only two did the elevation exceed twice the normal level.

TABLE 2. *Extent of Infarction as it Relates to Region of Occlusion*

Extent of Infarction	Region of Occlusion (Fig. 2) 1	2	3	4
Short segment of small intestine or colon	1	0	1	11
Most of the small intestine	7	4	11	0
Most of the small intestine and right colon	10	7	6	0
Most of the small intestine, right and transverse colon	17	7	7	0
Most of the small intestine and colon to sigmoid	7	4	0	0

TABLE 3. *Diagnosis as it Relates to Region of Occlusion (Numbers in Parentheses Represent Survivors in Each Category)*

	Region of Occlusion (Fig. 1) 1	2	3	4
Thrombi	40 (1)	3 (0)	2 (0)	1 (1)
Emboli	3 (0)	21 (2)	22 (6)	8 (5)
Total	43 (1)	24 (2)	24 (6)	9 (6)

Operative Management

Table 5 outlines the surgical management of all patients in the series. In nine, no operation was performed. In eight, this decision was based on the fact that whatever could be done for the infarction, the patient was already moribund. One of these patients was found at postmortem examination to have an embolus in a major jejunal branch of the SMA which had caused symptoms of intestinal ischemia but not actual infarction. In the ninth patient, an embolus was demonstrated by angiography, but infarction was not suspected. After undergoing coronary angiography by the femoral route, the patient had abdominal pain and bloody diarrhea. When this persisted, he was readmitted to the hospital. Selective angiography showed peripheral occlusion of a jejunal branch of the SMA (Fig. 3). He recovered completely. These two patients were the only two in the series who had proven emboli without infarction and are of special interest because of this.

Twenty-six patients had an exploratory laparotomy with neither resection nor attempt at revascularization. In 23, this decision reflected the extensiveness and

TABLE 4. *Diagnosis as it Relates to Extent of Infarction*

Extent of Infarction	Diagnosis: Thrombi	Emboli
Short segment of small intestine or colon	1	12
Most of the small intestine	8	14
Most of the small intestine and right colon	8	15
Most of the small intestine, right and transverse colon	20	11
Most of the small intestine and colon to sigmoid	9	2

TABLE 5. *Surgical Management*

Procedures	Survivals	Deaths	Total
No operation	1	8	9
Exploratory laparotomy	0	26	26
Resection	5	11	16
Revascularization	6	31	37
Revascularization and resection	3	12	15
	15	88	103

apparent irreversibility of the infarction. In the other three, the absence of hemorrhagic infarction led to the erroneous conclusion that revascularization was not necessary. In one, it was noted that there were no pulses in the SMA or in its branches. The patient died eight days later of mesenteric infarction. The autopsy showed thrombosis of the SMA and a patent vessel distal to this. In the second, faint pulses were present in the branches of the SMA, but the patient died ten days later of extensive mesenteric infarction. Again, thrombosis of the origin of the SMA was found at autopsy. In the third, pulses were diminished, but the intestine was viable. The patient died ten days later with the finding of an SMA embolus and extensive infarction. In all three cases, the preoperative diagnosis had been mesenteric infarction, and the error with respect to the necessity for revascularization was made by an experienced surgeon. An excellent possibility for a successful outcome was forfeited in each instance.

Resection without any attempt at revascularization was performed in 16 patients, five of whom survived. All five survivors had occlusions in region 4 (Fig. 2). Three had emboli to the terminal portion of the SMA. One had an embolus to the MCA. The fifth, a 63-year-old woman, had thrombosis of the terminal portion of the SMA. There was severe atherosclerotic involvement of this area and infarction of a 15 cm segment of the terminal ileum. The remainder of the SMA was normal to palpation, and subsequent angiography showed no other involvement of the vessel by atherosclerotic disease. No possible clue to this curious pattern of atherosclerotic disease could be found other than the patient's history of having received heavy external beam x-ray therapy to the lower abdomen two years before in treatment of a carcinoma of the cervix. Of the 11 patients with a resection who did not survive, only three had occlusion in region 4, and all three had multiple other emboli to intra-abdominal vessels. The others had embolic or thrombotic occlusion in regions 1 or 2. Thus, five of eight patients with peripheral occlusion survived with a resection alone, whereas none of the eight with central occlusion did so.

Embolectomy was carried out in 31 patients, being combined with resection in 12. Eight patients survived (26%). Salvage of all or part of the ischemic intestine was credited to embolectomy in 19 patients. In two, improvement was questionable, and in ten, the intestinal injury proved totally irreversible. Of the 31 patients, peripheral mesenteric pulses were restored in 29.

In all but one case, the SMA was exposed inferior to the mesocolon and distal to the MCA. The exception was a case in which the SMA was exposed at its origin. In almost every instance, a longitudinal arteriotomy was used. The technical problems encountered in performing the embolectomy included the presence of peripheral thrombus and difficulty in closing the arteriotomy without narrowing the vessel. Thrombus had propagated more than 1 cm beyond the embolus in nine of the patients (29%). In seven, this was successfully cleared with Fogarty embolectomy catheters. In two of these, a second more peripheral arteriotomy was

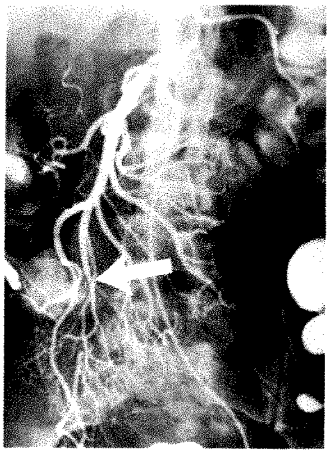

FIG. 3a. Arrow indicates site of occlusion of superior mesenteric artery distal to origin of ileocolic artery by small embolus.

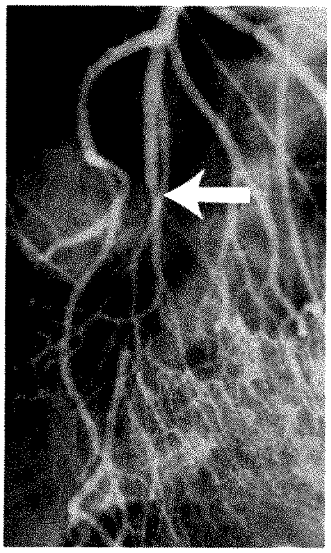

FIG. 3b. Detailed view of Figure 3a.

needed to accomplish this. In two patients, it could not be cleared. One complication was recorded as a result of the use of the Fogarty catheter. In this patient, the distal SMA was ruptured. Ligation of the vessel at that site with resection of a short segment of ileum was necessary. Difficulty in closing the SMA arteriotomy was encountered in three patients. In two, a short endarterectomy was needed, and in the third, a patch graft was utilized to widen the vessel.

Several complications were recorded in embolectomy of the SMA. The most frequent was thrombosis at the site of arteriotomy. This complication was noted in five patients (17% of those in whom peripheral pulses were restored by embolectomy). In three patients, thrombosis occurred within 48 hours. In the other two, it developed seven and 15 days after embolectomy. In both, there was a recurrence of the original symptoms at the time of thrombosis. In the first, the complication was confirmed by angiography (Fig. 4b). A successful thrombectomy with resection was performed. Thrombosis without infarction developed four weeks later (Fig. 4c). The patient survived. In the second, a successful thrombectomy with resection was performed, but the patient died six weeks later of a cerebral abscess.

Two patients had hemorrhage from the SMA arteriotomy. One occurred at 12 days in a patient receiving warfarin sodium. It was managed by resuture of the arteriotomy, and the patient recovered without sepsis

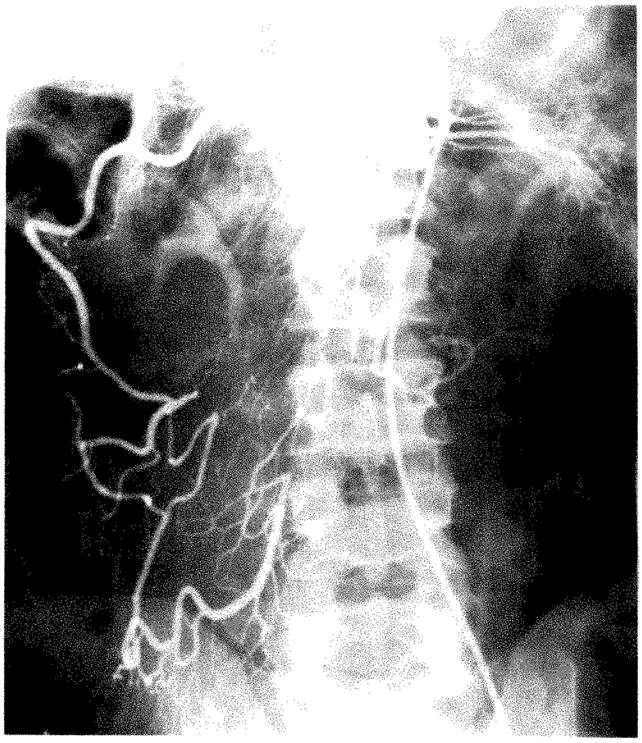

FIG. 4b. Thrombosis at arteriotomy site one week later.

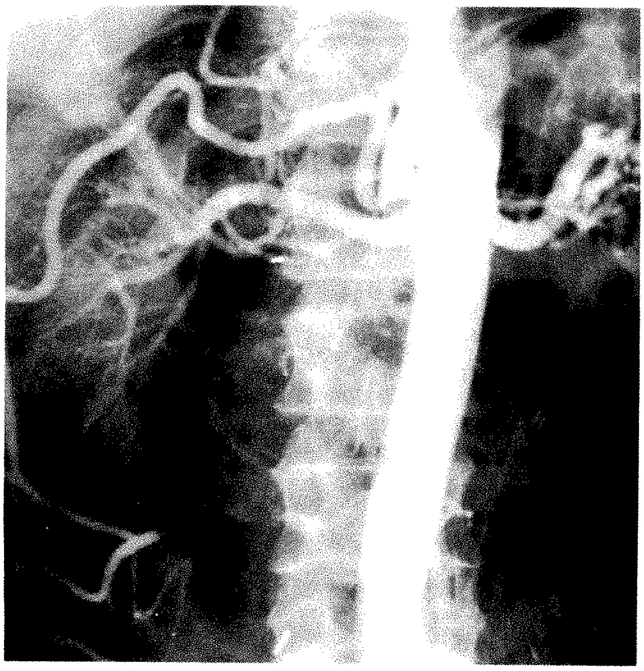

FIG. 4a. An embolus just beyond origin of MCA.

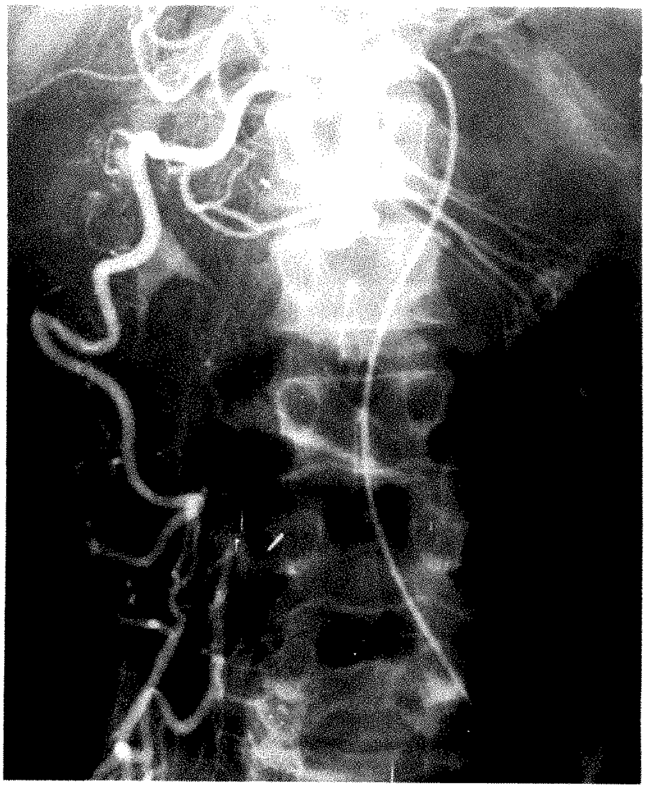

FIG. 4c. Rethrombosis at arteriotomy site four weeks later.

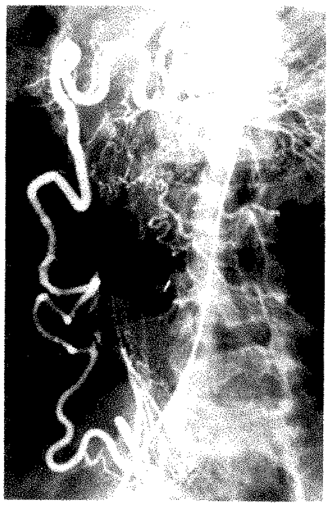

FIG. 5a. A false aneurysm of the superior mesenteric artery (arrow) one year after embolectomy and thrombectomy.

and lived for several years. The second occurred in the patient who had a successful thrombectomy seven days after the initial embolectomy and rethrombosis four weeks later. The patient was receiving heparin. The resulting retroperitoneal hematoma was managed without reoperation. An arterial fistula subsequently developed into the transverse colon. This was managed by ligation of the SMA at the fistula site and resection of the transverse colon. The patient developed a false aneurysm of the SMA (Fig. 5). He eventually died as a consequence of rupture of this aneurysm.

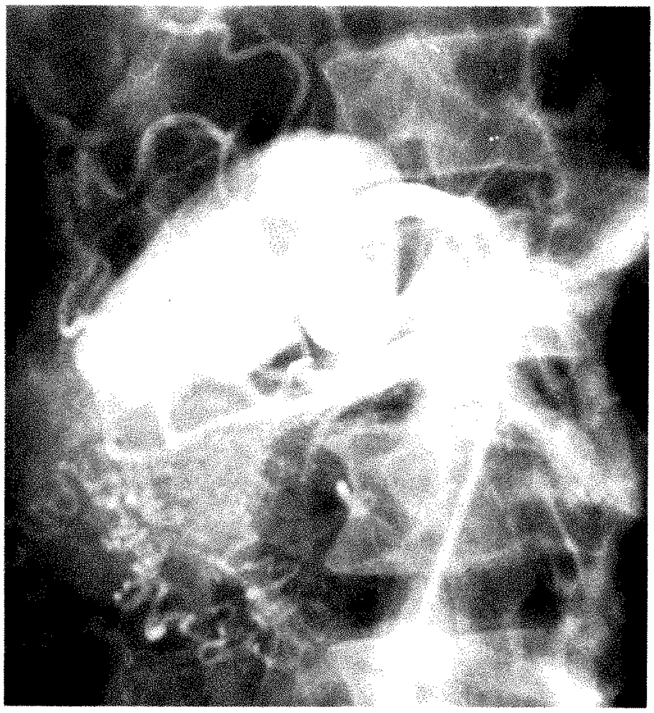

FIG. 5b. At time of rupture eight months later. The resultant hematoma occluded the large middle colic artery seen in Figure 5A.

Two patients developed complications related to the mesentery of resected segments of ileum. One had bleeding from several vessels in the mesentery. Reoperation with ligation of these vessels was necessary 24 hours after the embolectomy and resection. The second required resection of infarcted mesentery seven days after embolectomy and small bowel resection. This patient recovered.

Though all patients showed evidence of gastrointestinal hemorrhage during the days after embolectomy, in only two was the bleeding massive. The first patient required multiple transfusions for this complication during the four weeks after embolectomy. The second had persistent severe diarrhea after a successful embolectomy without intestinal resection. Four weeks after the embolectomy, massive intestinal hemorrhage occurred and a selective arteriogram showed the source to be the distal jejunum (Fig. 6a). A resection was performed with the finding of mucosal ulceration and regeneration. Three days later, bleeding recurred, and this time the source was shown to be the cecum (Fig. 6b). When a pitressin infusion failed to stop the bleeding, another resection was performed with the same pathologic findings. Bleeding did not recur, but the patient died two weeks later of respiratory and renal failure.

Other direct complications included prolonged diarrhea in several patients and one instance of jejunocutaneous fistula. A wide array of less direct complications were recorded. These were of the kind that would be expected with major operations in an aged and very ill population but were not related specifically to the embolectomy.

Eleven patients who had embolectomies underwent re-exploration during the initial 48 postoperative hours because of the question of persistent or new infarction. In six, infarction required resection. In the other five, the residual intestine was found to be entirely viable.

Revascularization was attempted in 21 patients with SMA thrombosis, being combined with resection in one patient. There was one survival. This patient had an iliac to SMA bypass graft when thromboendarterectomy proved impossible. In only six of the 21 patients did revascularization appear to result in salvage of ischemic bowel.

A technically satisfactory thromboendarterectomy was accomplished in 15 patients. An arteriotomy distal to the MCA was used in all. One patient required two additional peripheral arteriotomies to complete the endarterectomy. A patch graft at the arteriotomy site was required in three patients to avoid narrowing the vessel. No attempts were made to carry out an endarterectomy by exposure of the SMA at its origin. Adequate restoration of peripheral flow was accomplished in only nine of the 15 patients by endarterectomy alone.

Thrombosis more than 1 cm distal to the arteriotomy was found in four of the 21 patients. Use of the embolectomy catheter allowed successful removal of the peripheral thrombus in three. In the fourth, it was impossible, and the attempt at revascularization had to be abandoned.

Analysis of the results with respect to continued patency of the thromboendarterectomized segment was possible in 13 of the 15 patients. The vessel thrombosed within 48 hours in seven and at 11 and 13 days in two. In the other four patients, it remained patent, but all died within 48 hours. This high rate of failure points to the relative uselessness of thromboendarterectomy by the methods described here in the management of the patient with SMA thrombosis.

Reoperation was performed within 48 hours in eight patients. In seven, the finding was of extensive intestinal infarction. In one, the residual intestine was viable and the vessel patent, but this patient died of rethrombosis and infarction 11 days later.

Four patients had bypass grafts from an iliac artery to the SMA. One died intraoperatively. One had placement of a Dacron® bypass graft after endarterectomy and dilatation failed. The graft remained patent, but the patient died 48 hours later. One had placement of a Dacron graft after the proximal portion of the SMA disintegrated during thromboendarterectomy. The graft was found to be thrombosed when the patient died eight hours later. One had placement of a bypass graft using a segment of reversed saphenous vein after endarterectomy proved impossible. This patient was the only survivor of those with revascularization for thrombosis, and he remained alive and well at the time of our study four years later.

Second Look

Analysis of the records of patients with revascularization of the SMA showed 36 to be possible candidates for an early elective re-exploration to determine viability of the residual intestine. In 17, this was not considered necessary. The subsequent course justified the decision in 14. Three would have benefited from the second operation. A second look was planned by the surgeon in 19 patients. The indication in all was the presence of questionably viable segments of intestine at the time of closure. In addition, segments of clearly infarcted bowel had been left for later resection in three. Four patients died before the second look was performed. Two of these were among the three with nonviable segments of intestine. Fifteen patients thus

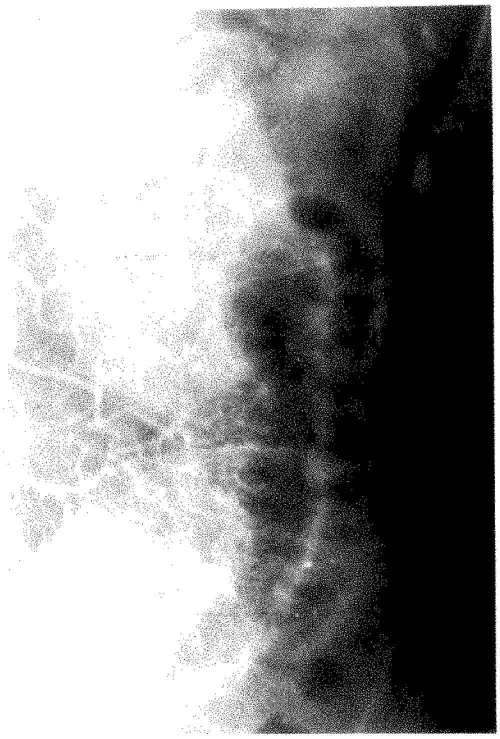

FIG. 6a. Jejunal hemorrhage (arrow) four weeks after SMA embolectomy.

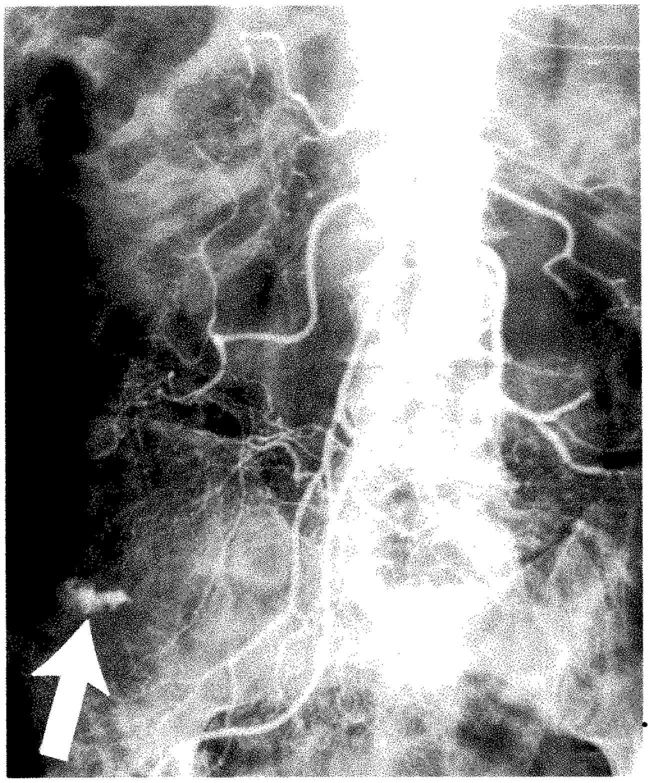

FIG. 6b. Cecal hemorrhage three days later (arrow).

underwent a planned second look operation between 12 and 36 hours after the initial procedure.

Eight of the 15 patients undergoing a second look required a bowel resection, and the operation enhanced their chances for survival. One survived. One patient was found to have infarction of the omentum. This was resected, but the patient did not survive. Another had thrombosis of the SMA. Thrombi were removed from the artery, but subsequent rethrombosis resulted in the patient's death. In four patients, the findings were negative. One of these survived. One patient was already moribund and died during the second look operation. No complications could otherwise be attributed to the second look operation.

In summary, the decision to perform the operation or not to do so was usually correct when the indication for a second look was the question of intestinal viability at the completion of the operation. Of the 17 candidates who did not have the operation, in only four would it have been beneficial. Of the 15 who did, only four did not profit from it.

Angiography

Angiography became readily available for clinical evaluation of patients with acute emergencies during the last four years included in this study. Eighteen arteriograms were done in 13 patients. In 11 patients, the study was performed to further evaluate symptoms thought to reflect intestinal ischemia. Six of these patients survived. In only two, however, did the study lead to an operation that had not already been planned. In several, the operation was more expeditious and better designed than it would have been had the precise site of occlusion not been known. This was a contribution to overall management. The high rate of survival of this group compared to that of the entire series also reflects a relatively younger age and the fact that few had irreversible infarction or were moribund, and it cannot be entirely attributed to angiography. In one patient, as already noted, an operation was avoided since the embolus was in a jejunal branch and an interval of several days had already passed without clinical evidence of infarction. Of the two patients in whom no operation was scheduled, one had an aortogram performed following a closed mitral valvuloplasty in the evaluation of renal shutdown. Renal artery emboli were shown as was an unsuspected SMA embolus. In the other, arteriography was performed seven days after the onset of abdominal pain. Although a vascular cause was thought unlikely, an embolus to the SMA was shown.

Two patients were studied after revascularization. In one, because the reconstruction of the SMA was thought questionable, angiographic study was performed in lieu of a second look operation. Thrombosis was demonstrated. In the second, previously mentioned, recurrence of symptoms at seven days and again at five weeks following embolectomy was found to be due to thrombosis at the site of arteriotomy. Both studies were judged useful.

Finally, three studies were done for massive gastrointestinal bleeding in the postoperative period. The findings have already been mentioned. One patient had an SMA to transverse colon fistula incorrectly diagnosed as a fistula to the duodenum in the interpretation of the study. In the second patient, the bleeding site was found on two separate occasions to lie in segments of revascularized intestine. All three studies were obviously of great value in the management of patients.

Special Considerations

Most emboli were deemed to have come from organized thrombi. Six, however, were composed of atherosclerotic debris and were therefore of the type sometimes termed cholesterol emboli. All were iatrogenic in the sense that the emboli in two resulted from angiographic studies and in the other four, they followed resection of the abdominal aorta. In three cases, there was a single embolus. One resulted from a coronary angiogram performed via the femoral route (Fig. 3). The other two were discovered before the abdomen was closed following resection of an abdominal aortic aneurysm. In none of these three cases were other emboli discovered, but in the other three, there were multiple small emboli. In one patient, an abdominal aortic angiogram had been performed, again via the femoral approach. The other two had had resection of an abdominal aortic aneurysm. All three had infarction of a segment of small intestine or right colon, but in all there were infarcts of other intra-abdominal structures as well. In each case, renal failure was the final cause of death. In none of the six cases with atherosclerotic emboli had there been a departure from the usual techniques of angiography or of handling and clamping the aorta. No means of avoiding such emboli can therefore be suggested from the study of these cases.

Five of the many patients with non-occlusive infarction who were excluded from this series should be mentioned. Two with 40% narrowing of the SMA had infarction of the small intestine and right colon following an acute myocardial infarction. A third with 95% narrowing developed infarction in the same area in the absence of any other apparent contributing factor. A fourth with 30% narrowing of the origin of the SMA developed infarction from the left transverse colon to the rectum with acute occlusion of the IMA. The fifth patient, who had long-standing atherosclerotic occlusion of the origins of the CA and IMA and a 90% narrowing of the SMA, developed infarction from the stomach to the rectum without apparent other cause. In all five cases, chronic partial occlusion of the SMA thus contributed to intestinal infarction in the absence of acute occlusion of the SMA itself. Revascularization of the SMA can, perhaps, contribute to survival of such patients despite the absence of complete occlusion.

Discussion

In an effort to gain a balanced and clinically applicable overview of the management of patients with SMA occlusion, all patients seen over a ten year period who had or, because the diagnosis was suspected before the occlusion proved fatal, could have had a surgical approach to their disease have been included in this series. The spectrum ranges from two patients who had a documented embolus without infarction to 31 who were moribund at the time of diagnosis. Of all the patients undergoing laparotomy, the injury to most or all of the involved bowel was judged to be reversible in about one half. In the others, resection was the only possible surgical treatment. Though conceivably, earlier diagnosis could favorably affect this rather dire picture, at the present time, only angiography offers any practical means for improvement. Reports of its application are hopeful and supported somewhat by the experience reported in this paper, but one cannot yet judge its impact on overall salvage. The median age in this series was 70 years, and few of the older patients were free of significant unrelated medical conditions that would greatly magnify the risk of any major emergency operation. Continued progress in the management of these problems also can contribute to increased survival.

Although the presence of occlusion of the SMA has been used to separate the patients reported in this paper from others with mesenteric infarction, this is in one sense a false distinction. Because of the unique collateral circulation of the small and large intestine, channels for preservation of viability exist in all cases. They are adequate in most patients with slowly developing occlusion of the SMA and in almost all those in whom there is even acute occlusion of the IMA. Thus, the factors of central perfusion pressure and peripheral arterial spasm have an important contributing role in every case. Despite this, those patients with a more central site of occlusion do tend to have more extensive areas of infarction and are shown to have a worse prognosis. In comparing mortality or rate of success by new approaches in the future, this data suggests the importance of classifying the site of occlusion as well as the incidence of irreversibility. Even a modest salvage rate for patients with occlusion in region 1 (Fig. 2) would represent a genuine advance (Table 3) whereas survival for patients with occlusion in region 4 should be routine even by present management. Some of these patients will, indeed, not develop infarction even with occlusion.

Resection without attempt at revascularization is the best operative approach initially in patients with occlusion in region 4 (Fig. 2). In this series, it resulted in survival of all such cases except for three with other intraabdominal infarcts from multiple emboli of atherosclerotic material, and even in these, it provided a successful solution to the problem of mesenteric infarction. With occlusion in regions 1, 2, and 3, resection without revascularization does not seem a useful approach even when combined with temporary or permanent intravenous alimentation. This is not to say, however, that such alimentation does not make an important contribution to survival when it is combined with revascularization and resection in patients with extensive infarction.[3]

The deceptive findings at the time of laparotomy in early cases of mesenteric infarction are worthy of emphasis. Older studies described two kinds of infarction—ischemic and hemorrhagic. In fact, they are usually the early and late stages in the evolution of the same pathologic process. In the ischemic phase, the intestine appears avascular, but faint peripheral pulses may be palpable and peristalsis is often present. It is important to palpate the main trunk of the SMA for a forceful pulse as the residual circulation may be only collateral in origin. It should be exposed and explored in questionable cases. Even the most experienced surgeon may attribute marginal findings to systemic hypotension or to arterial spasm thereby forfeiting an opportunity for complete intestinal salvage by revascularization. Angiography and elective re-exploration can both contribute to the early postoperative management of such patients.

The technique of revascularization for patients with emboli is well known. The vessel should be exposed in the small bowel mesentery inferior to the transverse mesocolon and distal to the origin of the middle colic artery. A longitudinal arteriotomy is preferred both because it lends itself to easy closure and because it can be used as the site for anastomosis of a bypass graft, if this becomes necessary. The Fogarty embolectomy catheter can be used to extract the embolus when it is not found at the site of the arteriotomy as well as to clear the vessel of distal thrombus. The mesenteric vessels are easily ruptured by the catheter and special care should be exercised in its use. Closure of the arteriotomy by direct suture without significant narrowing is almost always possible. In only three of 31 patients in this series was a local endarterectomy or a patch graft necessary to achieve this. By the use of this technique for embolectomy, satisfactory peripheral flow was restored in 29 of 31 patients thus establishing the efficacy of this approach.

In contrast to embolectomy, thromboendarterectomy by the approach we have employed had an unacceptably high rate of failure. The SMA was exposed at the same site as for embolectomy, and a "blind" proximal endarterectomy performed. Inflow could not be restored in six of 21 patients. Furthermore, the site of endarterectomy thrombosed in seven of the 13 patients in whom the necessary observations could be made in the first 48 hours postoperatively. Thus, in only six to eight of the 21 patients could the method of revascularization be judged to have been successful.

Brittain and Earley described thromboendarterectomy by another approach with patient survival in three of four cases.[2] These authors exposed the SMA at its origin posterior to the pancreas, approaching it through the omentum and lesser sac. The origin of the vessel was included in the proximal occluding clamp, and the endarterectomy was carried out under direct vision. Though this exposure is difficult or impossible in some patients from an anterior abdominal approach because of the high origin of the SMA with respect to the body of the pancreas, it deserves further clinical evaluation. Another method to be considered is the placement of a bypass graft from the aorta or iliac artery to the SMA. Four patients reported in this paper had this procedure. Though only one patient survived, in a second, the graft remained patent and functioned satisfactorily. Because of the high risk of infection of the bypass when an intestinal resection is necessary, a reversed segment of saphenous vein would be the preferred material for the graft.

Because of the high failure rate of endarterectomy performed through a distal arteriotomy, intraoperative differentiation between thrombosis and embolus before opening the SMA is important. Table 3 suggests that the absence of a pulse in the origin of the vessel almost invariably means that thrombosis is the cause of occlusion. Preoperative angiography can also be expected to be of great help, since the origin of the vessel is so seldom the site of lodgment of an embolus.

The peripheral propagation of thrombus in acute occlusion of the SMA has been one of the causes of failure of revascularization. Such propagation was found in nine of 31 patients with emboli and in four of 21 with thrombus. In all but two of these 13 patients, it was successfully cleared with the Fogarty catheter. It was also possible to "milk" clots out of smaller vessels. Small residual peripheral blocks are sometimes tolerated, but their presence may contribute to irreversibility of infarction in short segments, leading to the necessity for resections.

Thrombosis at the arteriotomy site, when it occurs within the first 48 hours after revascularization, should be considered a complication of technique. It was observed in three patients after embolectomy and in seven after endarterectomy, though in some of the latter group, it undoubtedly originated at the site of endarterectomy rather than arteriotomy. It is possible that taking measures to maintain a high flow through the SMA by preventing arterial spasm in its distribution may avoid this complication. Boley and associates have suggested the intra-arterial infusion of papavarine as one means of achieving this.[1] This may be a very substantial contribution to the management of these patients. Late thrombosis at the arteriotomy site was observed in four patients, one of whom also had a second delayed thrombosis 30 days after a successful thrombectomy. The late occlusions occurred at 7, 7, 11, 15, and 30 days after the preceding vascular procedure. Awareness of this complication, which in some instances may represent re-embolization, is important since re-establishment of flow is usually feasible. In each case, reocclusion precipitated symptoms identical with those of the original episode. The incidence of late thrombosis has no ready explanation but does suggest the possible importance of careful postoperative anticoagulation even in patients whose original diagnosis was thrombosis.

Another complication recorded in two patients was delayed hemorrhage from the arteriotomy. In one, it occurred 12 days after an embolectomy in a patient receiving warfarin. The vessel was resutured. There was no further bleeding, and the patient recovered without subsequent complications including suture line sepsis. In the second, a patient receiving heparin, hemorrhage occurred four weeks after embolectomy and subsequent thrombectomy at the arteriotomy site. This patient subsequently developed a fistula from the SMA to the transverse colon and still later, a false aneurysm. Though it could not be proved, it is entirely possible that sepsis in the arterial suture line was responsible for these complications. This was the only case in which arterial sepsis was suggested, but fear of this complication is an important incentive to the intraoperative and postoperative use of carefully selected parenteral antibiotics.

Revascularized intestine may require several weeks to heal. This phase of recovery is usually marked by diarrhea. Mucosal ulcers and intraluminal bleeding are also characteristic. Several patients required transfusion. Only one had massive hemorrhage of life threatening proportions. This patient twice required segmental bowel resections for the control of bleeding. Though angiography was helpful in demonstrating the source, bleeding was not controlled by a pitressin infusion in the one instance in which it was tried. Strictures have been recorded as a late complication of revascularization, but none were observed in this series.

Shaw first proposed the use of elective abdominal exploration after SMA embolectomy.[8] He suggested laparotomy when the status of segments of intestine was questionable but resection undesirable. His approach continues to be applied in our hospital. The question as to whether the "second look" should be used in all patients after revascularization is unanswered. The risk of an unnecessary laparotomy is low and a correct judgment as to its desirability cannot always be made at the initial operation. Despite these factors and the somewhat equivocal experience reported in this paper, the use of laparotomy in every case is probably not indicated. There can be no question, however, that the early postoperative course cannot be used as an indication for its necessity but that the decision to re-explore or not should be made at the time of closure. It is unwise and often fatal to leave clearly nonviable segments of intestine for later resection.

The future role of angiography in the management of mesenteric infarction is unresolved. Recent reports suggest that its routine use may have a significant impact in reducing mortality.[1,4] Certainly, it should be used in all cases preoperatively when there is a question as to diagnosis and when unacceptable delay will not result. Almost invariably, in addition to the diagnosis, such studies will provide anatomic information of value for the surgeon. This may be offered as a reason for the use of angiography in all case even when the diagnosis is known. There is no question as to its value in the management of recurring symptoms of ischemia after revascularization and secondary intestinal bleeding. In addition to these, the use of angiographic techniques for continued perfusion of the mesenteric arterial tree to relieve spasm may prove helpful in the management and prevention of both occlusive and nonocclusive infarction. Boley's paper[1] is of particular interest because of his vigorous advocacy for the use of these diagnostic and therapeutic techniques.

Conclusions

The age and infirmity of the patients and the significant incidence of extensive and irreversible intestinal injuries make it unlikely that mortality can be reduced below 50% in a series such as that described in this study. Despite this, a considerable improvement over that reported can be achieved. Areas for special attention are apparent. These include the more extensive use of angiographic techniques before and after surgery, progress in the intraoperative assessment of etiology and selection of procedures, technical advances in revascularization, and the anticipation and better management of direct complications such as arteriotomy hemorrhage, rethrombosis at the site of embolectomy or thromboendarterectomy, and intestinal bleeding. Routine postoperative systemic anticoagulation must be considered even in patients without emboli. Finally, increasing skill and capability in the management of alimentation and multiple system failure can be expected to make a further contribution toward survival.

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A Multifactorial Analysis of Melanoma:

Prognostic Histopathological Features Comparing Clark's and Breslow's Staging Methods

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A multifactorial analysis was used to identify the dominant prognostic variables affecting survival from a computerized data base of 339 melanoma patients treated at this institution during the past 17 years. Five of the 13 parameters examined simultaneously were found to independently influence five year survival rates: 1) *pathological stage* (I vs II, p = 0.0014), 2) lesion *ulceration* (present vs absent, p = 0.006), 3) *surgical treatment* (wide excision vs wide excision plus lymphadenectomy, p = 0.024), 4) melanoma *thickness* (p = 0.032), and 5) *location* (upper extremity vs lower extremity vs trunk vs head and neck, p = 0.038). Additional factors considered that had either indirect or no influence on survival rates were clinical stage of disease, age, sex, level of invasion, pigmentation, lymphocyte infiltration, growth pattern, and regression. Most of these latter variables derived their prognostic value from correlation with melanoma thickness, except sex which correlated with location (extremity lesions were more frequent on females, trunk lesions on males). This statistical analysis enabled us to derive a mathematical equation for predicting an individual patient's probability of five year survival. Three categories of risk were delineated by measuring tumor thickness (Breslow microstaging) in Stage I patients: 1) *thin* melanomas (<0.76 mm) were associated with localized disease and a 100% cure rate: 2) *intermediate* thickness melanomas (0.76–4.00 mm) had an increasing risk (up to 80%) of harboring regional and/or distant metastases and 3) *thick* melanomas (≥4.00 mm) had a 80% risk of occult distant metastases at the time of initial presentation. The level of invasion (Clark's microstaging) correlated with survival, but was less predictive than measuring tumor thickness. Within each of Clark's Level II, III and IV groups, there were gradations of thickness with statistically different survival rates. Both microstaging methods (Breslow and Clark) were less predictive factors in patients with lymph node or distant metastases. Clinical trials evaluating alternative surgical treatments or adjunctive therapy modalities for melanoma patients should incorporate these parameters into their assessment, especially in Stage I (localized) disease where tumor thickness and the anatomical site of the primary melanoma are dominant prognostic factors.

MELANOMA IS A CAPRICIOUS malignant neoplasm with many variables that seem to influence survival. Factors that have been described with prognostic value include such clinical parameters as stage of disease, sex, race, location and size of lesions, hair color, surgical treatment, pregnancy, and immunocompetence, as well as pathological parameters such as growth patterns, ulceration, blood vessel invasion or lymphocyte infiltration.[1,3,6,7,10,12,13,15,18,26] An important biological concept influencing prognosis is the correlation between increasing melanoma invasion into the skin and risk of metastases, as first described by Allen,[1] Lund,[17] Lane,[16] Peterson,[19] Mehnert[18] and others. In 1969, Clark and colleagues[5,6] defined levels of microinvasion and proposed a classification that has now been widely adopted. This system categorized melanoma by the maximum depth of penetration into different levels of the dermis or subcutaneous tissue. Breslow[3,4] suggested in 1970 that tumor thickness was a reliable criterion of prognosis. He measured the vertical dimensions of the melanoma in millimeters with an ocular micrometer as an alternative, and perhaps easier method for correlating melanoma invasion with survival. Others have corroborated that the histological level of melanoma invasion (as staged by Clark) and the measured lesion thickness (as advocated by Breslow) are very important deter-

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* Supported by grants from the National Institute of Health (CA 13148, CA 19657).

Submitted for publication: December 22, 1977.

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minants of survival and helpful guides for patient management.[7,9,10,12,13,22,26]

Most previous studies of melanoma patients have compared prognostic variables using single factor statistical analyses. Conflicting results from among these studies may have been influenced by intercorrelations of the variables examined, such as sex and melanoma location, or from additional factors that were not accounted for, such as tumor thickness. When numerous factors appear to influence survival rates, a multifactorial (or multivariate) analysis is necessary to delineate the dominant variables with independent predictive value. In this study, a multifactorial analysis was utilized to simultaneously compare 13 clinical and pathological features of melanoma. The computorized data base for this statistical analysis was compiled from a detailed retrospective/prospective study of over 339 patients treated at this institution during the past 17 years. This report focuses upon the histopathological features of 211 primary cutaneous melanomas for their potential prognostic value.

Patient Population and Methods

Patient Population

We examined the hospital records of 339 melanoma patients registered between 1960 to 1977 by the Tumor Registry or the Pathology Department at the University Hospital and the Veteran's Hospital. Patient groups excluded from this analysis included: 12 patients whose records contained insufficient clinical information, 13 patients who had nodal metastases from unknown primary sites, 13 patients with shave biopsies extending to the deep margin and 90 patients whose original biopsy specimen could not be obtained for review. In the remaining 211 patients, we obtained the original histological slides and/or paraffin blocks of their primary cutaneous melanomas. The melanomas were all re-examined by one pathologist (TMM) who did not have knowledge of the clinical course in any of these patients. The surgical procedures were performed by two surgeons (WAM and CMB) for 86% of these patients. The primary melanoma was widely excised with a 4–5 cm margin, except where interdicted by anatomical barriers, such as on the face. Therapeutic node dissections were performed for all patients with suspicious nodal metastases (clinical Stage II). In patients with apparent normal regional nodes (clinical Stage I), the decision regarding elective lymphadenectomy vacillated during the years reflecting a changing concensus of national opinion regarding its efficacy; the histopathological staging did not influence this decision until recent years.

Records from melanoma patients were reviewed and the data recorded on standardized forms designed for computer analysis. Follow-up data was obtained from patient records and by telephone interviews with the patients, their families or their primary physicians.

Microstaging

Level of invasion (Clark's method). The primary melanomas were categorized according to Clark's classification (6) into Level II (into papillary dermis), Level III (through papillary dermis at interface with reticular dermis), Level IV (into reticular dermis) and Level V (into subcutaneous tissues). A polarizing light source in the microscope greatly enhanced the visual identification of thick collagen fibers in the reticular dermis. This enabled us to better discriminate Level III from Level IV lesions.

Tumor thickness (Breslow's method). The vertical dimension of each melanoma was measured from the top of the granular layer to the base of the tumor using an ocular micrometer.[3,4] In ulcerated lesions, the thickness was recorded from the base of the ulcer to the base of the tumor. In cases where the distance from the top of the granular layer to the base of the tumor was greater than the distance from the ulcer to the base, the larger value was recorded.

Definition of Pathological Terms

Growth pattern. Melanomas were classified by microscopic analysis into lentigo maligna, superficial spreading and nodular types as defined by Clark.[5] In addition, we separately classified the growth pattern of 28 melanomas as polypoid. These lesions had an exophytic pattern with more of their vertical growth located above the epidermis than into the dermis. The edges of these polypoid lesions were typically everted with the lateral margin extending above the epidermis.

Ulceration. Ulceration was defined as an interruption of the surface epithelium involved by the tumor.

Lymphocyte infiltration. This was categorized into three grades. Grade I was absent to mild lymphocytic infiltration around lesions, showing very few or small groups of lymphocytes at their periphery. Grade II was moderate lymphocytic infiltration represented by multiple foci of lymphocytes at the edge and beneath the lesion. Grade III represented a marked lymphocytic infiltration where the lymphocytes were confluent occasionally forming bandlike features.

Pigmentation. Pigmentation was present if melanoma cells and/or macrophages contained melanin pigment in their cytoplasm. Lesions were scored as depigmented if virtually all cells had no cytoplasmic melanin.

Regression. The criteria set forth by Smith were followed.[23] Signs of regression were recognized whenever there was increased vascularity with scattered melanin-laden macrophages in the dermis and signs of fibrosis. Typically the overlying epidermis in the area of regression lacked melanin pigment while pigment was recognized in normal epidermis.

Statistics

The UAB Melanoma Registry is an ongoing retrospective/prospective analysis of all patients with malignant melanoma treated at the University of Alabama Medical Center. Detailed clinical and pathological information was computerized to facilitate data management and statistical analysis. Survival curves were calculated based upon the method of Kaplan and Meier.[14] A generalized Wilcoxon test[11] was used to determine if significant differences existed between curves. Chi-square tests were also employed in statistical assessments where appropriate. In addition, the multiple logistic regression procedure proposed by Cox[8] was used in a multifactorial analysis of prognostic factors.

Actuarial survival curves were calculated from patients who died with known melanoma; those who died without evidence of disease were computed as alive without disease for the time interval from treatment to death. In this report, survival curves are drawn as solid lines to the point of longest survival prior to death from disease; the continued broken lines indicate the survival duration of patients remaining alive.

Results

Level of Melanoma Invasion (Clark)

The data base for patients analyzed by Clark's microstaging method is shown in Table 1. Increasing level of invasion correlated inversely with survival and with the presenting pathological stage of disease. The cumulative incidence curves (Fig. 1) demonstrates that virtually all Level II lesions had vertical dimensions less than 1.5 mm while all Level V lesions exceeded 1.5 mm in thickness. Level III and IV lesions were more diverse in their vertical growth.

The median thickness for Clark's II lesions was 0.6 mm (range 0.2–3.2 mm). The thickest lesion in this group was a polypoid melanoma. Level III lesions had a median thickness of 1.4 mm (range 0.5–8.0 mm) Level IV lesions had a median thickness of 2.8 mm (range 0.6–12.6 mm), 22% of these were less than 1.5 mm in thickness (Fig. 1). Level V lesions had a median thickness of 5.1 mm (range 2.1–25.0 mm); all measured more than 1.5 mm, while 65% were greater than 4 mm.

TABLE 1. *Data Base Using Level of Invasion (Clark) Microstaging*

	II	III	IV	V	Total (#)
Number of patients	36 (17%)	70 (34%)	75 (36%)	28 (13%)	209
A. Presenting pathological					
Stage I	35 (20%)	62 (36%)	60 (35%)	15 (9%)	172
Stage II	1 (3%)	7 (21%)	14 (41%)	12 (35%)	34
					p = 0.003*
B. Thickness					
<0.76 mm	27 (65%)	12 (28%)	3 (7%)	0 (0%)	42
0.76–1.49 mm	7 (16%)	23 (51%)	15 (33%)	0 (0%)	45
1.50–4.00 mm	2 (3%)	30 (39%)	35 (46%)	9 (12%)	76
>4.00 mm	0 (0%)	5 (11%)	20 (45%)	19 (43%)	44
					p < 0.0001
C. Growth pattern					
Lentigo maligna	4 (50%)	3 (38%)	1 (12%)	0 (0%)	8
Superficial spreading	19 (46%)	13 (32%)	8 (20%)	1 (2%)	41
Nodular	12 (9%)	47 (37%)	44 (35%)	24 (19%)	127
Polypoid	1 (4%)	7 (25%)	17 (61%)	3 (10%)	28
					p < 0.0001
D. Melanoma ulceration					
Absent	27 (25%)	43 (40%)	29 (27%)	8 (8%)	107
Present	3 (4%)	25 (30%)	38 (46%)	17 (20%)	83
					p < 0.0001
E. Pigmentation					
Absent	2 (7%)	9 (30%)	15 (50%)	4 (13%)	30
Present	32 (19%)	58 (35%)	53 (32%)	23 (14%)	166
					p = 0.172
F. Lymphocyte infiltration around primary					
Grade I	19 (13%)	46 (31%)	63 (42%)	22 (14%)	150
Grade II and III	14 (36%)	18 (46%)	5 (13%)	2 (5%)	39
					p = 0.171

* p values represent the statistical significance levels correlating level of invasion and each pathological parameter.

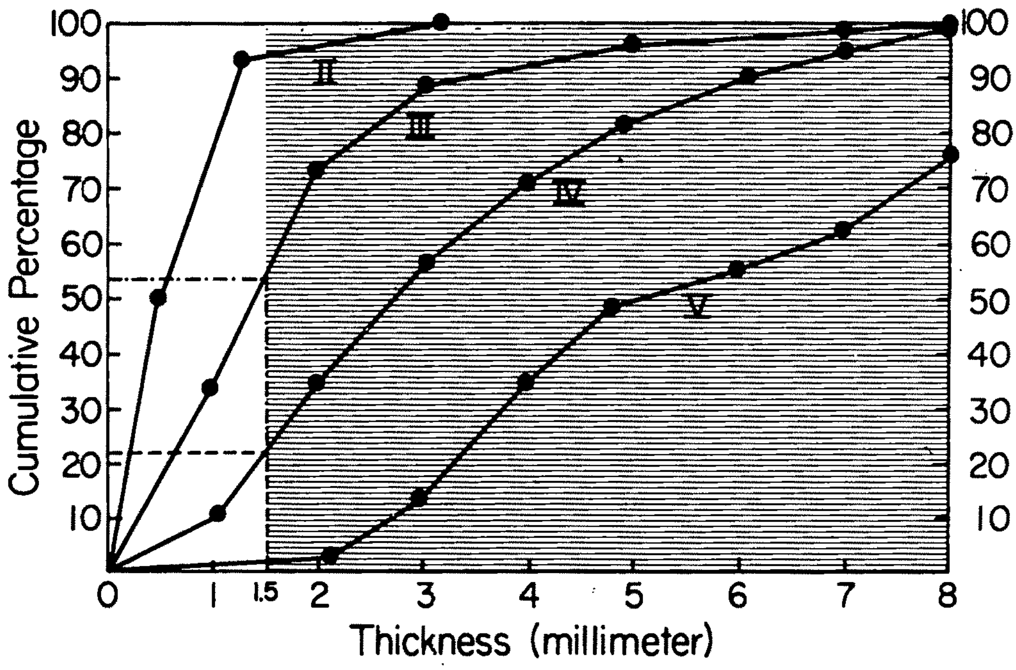


FIG. 1. Cumulative distribution of thickness measurements for each level of invasion (Clark's microstaging). As an example, 53% of Level III and 22% of Level IV melanomas had a thickness less than 1.5 mm (unshaded area).

Actuarial survival curves (Fig. 2A) show significant differences among all Clark's levels except Level II and Level III, which however, comprise 51% of the total patient population. Patients presenting with confirmed nodal metastases (pathological Stage II) had primary melanomas with twice the average thickness for each Clark's levels, compared with melanomas from patients with pathological Stage I disease. However, the Clark's level of invasion did not correlate with survival in patients presenting with pathologic Stage II disease. The number of pathological metastatic nodes and other parameters were overriding factors determining survival.

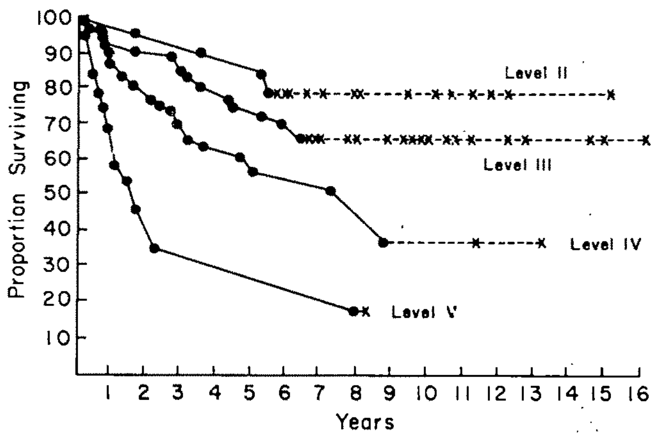
Melanoma Thickness (Breslow)

The data base for melanomas analyzed by Breslow's microstaging method is listed in Table 2. Numerous sets of measured thickness were examined for prognostic value (*e.g.*<1 mm, 1–4 mm, >4 mm), but none were found to have more discriminating value than those advocated by Breslow with one exception. For thicker lesions, we found more significant survival differences using 4 mm rather than 3 mm as demonstrated by actuarial survival curves (Fig. 2B). Three risk categories were identified. Patients with *thin melanomas* measuring 0.75 mm or less had localized disease. The only patient with pathological Stage II melanoma and a thin lesion was untreated for a year after misinterpretation of the biopsy, which was made correctly in retrospect when the patient subsequently presented with nodal metastases. Since our analysis was based primarily on re-examination of representative sections through the lesion rather than serial sectioning of the entire melanoma, it is possible that thicker areas may have existed in this specimen. Patients with *intermediate thickness melanomas* measuring 0.76–3.99 mm had increasing risk (up to 80%) of harboring regional and/or distant disease. Patients with *thick lesions*, exceeding 4 mm in thickness, had a very high risk (80%) of harboring distant metastatic disease, despite the fact that most had clinically undetectable metastatic disease at their initial presentation. Only one of 14 patients in this latter group survived more than five years. Patients presenting with pathological Stage II disease had thicker lesions than their Stage I counterparts (median thickness of 4.6 vs 1.6 mm respectively).

Comparison of Level vs Thickness as Prognostic Indicators

Figure 3A compares each level of invasion subdivided by thickness using actuarial calculations of five year survival rates. Within each level, there were gradations of thickness that influenced survival. For example, Clark's Level IV lesions measuring 0.76–1.49 mm had a 76% five year survival while thicker lesions (≥4.0 mm) had a 25% five year survival ($p = 0.02$). Similar discordance in five year survival figures was observed for each of the levels when subgrouped by thickness. Converse relationships were not observed when analyzing the sets of melanoma thickness subdivided by levels of invasion (Fig. 3B). For example, the five year survival for lesions measuring 1.50–3.99 mm was not significantly different for Level III, IV, and V lesions. To confirm these observations, we pooled the data from our clinical Stage I patients with that published by Breslow.[3] Within each Clark's level,

A. SURVIVAL CURVES BY LEVEL OF INVASION



B. SURVIVAL CURVES BY THICKNESS

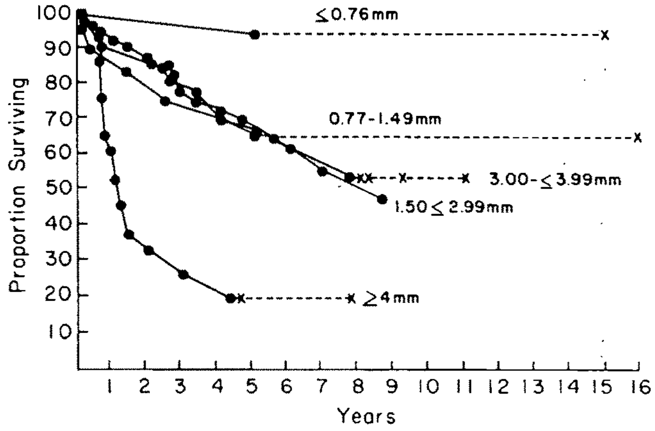


FIG. 2. Actuarial survival curves derived from microstaging. A) Clark's levels of invasion. The statistical differences between these levels were: II vs III ($p = 0.21$), III vs IV ($p = 0.07$), IV vs V ($p = 0.002$). B) Melanoma thickness. The statistical differences were: 0.76 vs 0.77–1.49 mm ($p = 0.006$), 0.77–1.49 vs 1.50–2.99 mm ($p = 0.84$) and 3.00–3.99 vs ≥ 4.0 mm ($p = 0.01$).

there were subgroups of different thickness with statistically significant differences in five year determinate disease-free rates (Table 3). However, within each thickness group, there were no subgroups of different Clark's level that influenced this rate significantly.

Growth Pattern

Survival curves for each of the 4 growth patterns of melanoma are shown in Figure 4A. Superficial spreading and lentigo maligna lesions had the best survival while polypoid lesions had the worst prognosis. The only statistically significant difference among these groups was between superficial spreading and polypoid lesions ($p = 0.001$).

Nodular melanomas with radial growth less than three rete pegs from the tumor constituted the majority (62%) of patients in our series. It is possible that some of these lesions may have been late superficial spreading melanomas with more lateral growth in unsampled sections of the slides. The median thickness for these lesions was 2.0 mm (1.5 mm for pathological Stage I disease, 4.4 mm for pathological Stage II). The majority (64%) had a thickness exceeding 1.5 mm while 72% were Clark's Level III or IV lesions (Tables 1 and 2). Five year survival in this group was 65%. There was no predeliction of nodular melanomas to any particular location on the body.

Patients with superficial spreading melanomas constituted 20% of the melanomas in our series. The median thickness for these lesions was 0.8 mm. A minority (24%) of patients had lesions exceeding 1.5 mm (Fig. 5). Almost half of the melanomas in this group were Level II lesions. Five year survival was 73%. The three deaths were all Clark's Level III lesions. Two of the three had lesions exceeding 1.5 mm.

Polypoid melanomas were the worse group prognostically. These constituted 13% of the total group. Their median thickness was 4.8 mm (3.6 mm for Stage I disease, 6.3 mm for Stage II disease). All lesions measured greater than 1.5 mm; 61% in fact measured greater than 4 mm (Fig. 5). The majority (61%) of these lesions were Clark's Level IV. Five year survival for the group was 47%.

There were 8 patients (4%) with lentigo maligna lesions. The median thickness was 0.6 mm. All patients presented with pathological Stage I disease. The five year survival was 71%. Both patients who died with metastatic disease had lesions exceeding 1.77 mm thickness.

Lymphocyte Infiltration

For patients with pathological Stage I disease, there was an inverse correlation with thickness and the magnitude of lymphocyte infiltrate around the primary melanoma lesion ($p = 0.003$). Patients with absent to minimal lymphocyte infiltration had a median 2.3 mm thickness, while those with a heavy lymphocyte infiltration had a median 1.1 mm thickness. There was no correlation of lymphocyte infiltration and thickness for patients with pathological Stage II disease. Grade II or III lymphocyte infiltration surrounding the melanomas was observed in 100% of patients with lentigo maligna lesions, 90% of those with superficial spreading melanoma and 60% of nodular melanomas. However, these differences among different grades of lymphocyte infiltration and thickness did not influence survival significantly (Fig. 4B).

Ulceration

The presence of ulceration on the microscopic sections of melanomas was a significant adverse determinant of survival (Fig. 4C). Patients with ulceration (42% of total group) had a five year survival rate of 52% while those without ulceration had a 77% five year survival rate ($p = 0.001$). There was a positive correlation of ulceration with thickness ($p < 0.0001$). The median thickness for patients with ulceration was 3 mm while those without ulceration had a median thickness of 1.3 mm. Lesions thicker than 1.5 mm were associated with an 80% incidence of ulceration. Likewise, more than 66% of patients with Clark's Level IV or V lesions had ulcerations (Table 1).

Pigmentation

Although only 18% of melanomas had evidence of depigmentation, this was also a significant adverse determinant of survival (Fig. 4D). Five year survival rate of patients without lesion pigmentation was 36% while those patients with pigmentation had a 69% five year survival rate ($p = 0.006$). Lack of pigmentation occurred more frequently in thicker lesions (Table 2, $p = 0.05$).

Regression

Only a small minority (17/170 patients) had evidence of lesion regression. This factor had no significant influence on survival ($p = 0.13$).

Age, Sex and Location

There was no significant correlation of age with histopathological features of melanoma. There was a trend for patients in the sixth and seventh decades, of life to have somewhat thicker lesions.

Melanomas in our series were almost equally divided between males and females. Females had a slightly better survival rate than males, although this was not a statistically significant difference when examined as a single parameter ($p = 0.479$). Lower leg lesions occurred predominantly in females (79%) while the majority of trunk lesions were in males (70%).

There were several histopathological features which correlated with location of the lesion. First, all lentigo maligna lesions were located on the face. Second, survival rates for trunk lesions were worse than lesions of head and neck, lower extremity or upper extremity. These differences were not statistically significant when analyzed as single parameters ($p = 0.354$).

Multifactorial Analysis

Prognostic factors analyzed for their influence on survival were: lesion thickness, Clark's level of invasion, ulceration, pigmentation, lymphocyte infiltration, growth pattern, regression, primary lesion sites, pathological and clinical stages, surgical treatment, age and

TABLE 2. *Data Base Using Tumor Thickness (Breslow) Microstaging*

	<0.76 mm	0.76–1.49 mm	1.50–3.99 mm	≥4 mm	Total (#)
Number of patients	42 (20%)	47 (23%)	78 (36%)	44 (21%)	211
A. Presenting pathological					
Stage I	41 (24%)	43 (25%)	66 (38%)	24 (13%)	174
Stage II	1 (3%)	2 (6%)	11 (32%)	20 (59%)	34
					$p < 0.0001$*
B. Level of invasion					
Level II	27 (73%)	7 (19%)	2 (8%)	0 (0%)	36
Level III	12 (17%)	23 (33%)	30 (43%)	5 (7%)	70
Level IV	3 (4%)	15 (21%)	35 (48%)	20 (27%)	73
Level V	0 (0%)	0 (0%)	9 (32%)	19 (68%)	28
					$p < 0.0001$
C. Growth pattern					
Lentigo maligna	4 (50%)	2 (25%)	2 (25%)	0 (0%)	8
Superficial spreading	24 (57%)	8 (19%)	9 (21%)	1 (3%)	42
Nodular	14 (11%)	32 (25%)	55 (43%)	26 (21%)	127
Polypoid	0 (0%)	0 (0%)	11 (39%)	17 (61%)	28
					$p < 0.001$
D. Ulceration					
Absent	32 (30%)	29 (27%)	38 (35%)	9 (8%)	108
Present	4 (5%)	12 (15%)	34 (41%)	32 (39%)	82
					$p < 0.0001$
E. Pigmentation					
Absent	2 (6%)	5 (16%)	13 (42%)	11 (36%)	31
Present	38 (23%)	37 (22%)	61 (37%)	30 (18%)	166
					$p = 0.051$
F. Lymphocyte infiltration					
Grade I	24 (16%)	29 (19%)	58 (39%)	40 (26%)	151
Grade II and III	14 (37%)	13 (34%)	9 (24%)	2 (5%)	38
					$p = 0.003$

* p values represent the statistical significance levels correlating tumor thickness and each pathological parameter.

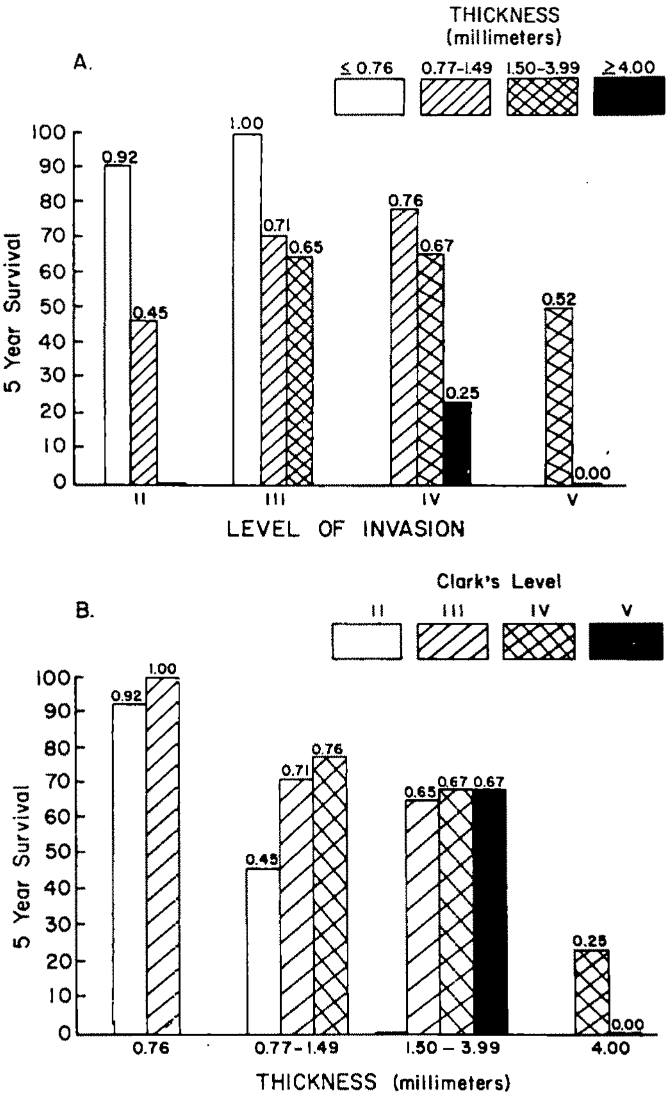


FIG. 3. Comparison of two microstaging methods: A) Levels of invasion subgrouped by thickness. There were statistically significant differences among thickness groups within each level of invasion. B) Thickness subgrouped by level of invasion. There were no statistically significant differences among the levels of invasion within each thickness group.

sex. Table 4 presents the relative importance of each single factor unadjusted for other factors. For example, the thickness of melanoma was highly predictive of five year survival ($p = <0.00001$) while the alternative surgical treatments (wide excision ± elective lymphadenectomy) did not influence survival ($p = 0.638$). A multifactorial analysis was then performed to examine the primary predictor factors that independently correlated with five year survival, while simultaneously accounting for the contribution of the other factors listed above. Each variable was analyzed in sequence for their additive prognostic value after the preceding factors had been accounted for. For example, when level of invasion was ranked in the first position followed by tumor thickness, the p values for each variable were 0.003 and 0.001 respectively. This indicated that the parameter of tumor thickness contributed additional prognostic information after level of invasion had been accounted for. On the other hand, when these variables were arranged in reverse order, thickness was a highly predictive factor ($p = 0.0002$), but level of invasion had no additional predictive influence after thickness was accounted for ($p = 0.7105$).

The influence of these factors on survival was examined using a cohort of 97 patients who survived more than five years. Based upon the model proposed by Cox,[8] a statistical (forward) selection procedure selected a subset of factors that was most predictive of five year survival. The subset consisted of the following five prognostic indicators (Table 5): pathological stage ($p = 0.0014$), lesion ulceration ($p = 0.006$), surgical treatment ($p = 0.024$), thickness ($p = 0.032$), and primary lesion site ($p = 0.038$). Each factor was adjusted for all other factors under analysis. Although several variables, such as clinical stage, Clark's level, pigmentation, and age were significant as single factor predictors (Table 4), they were excluded from the subset as secondary variables. On the other hand, surgical treatment and primary lesion site became significant prognostic variables after adjusting for other factors.

This statistical analysis enabled us to derive an equation (incorporating the factors in the selected subset) for predicting an individual patient's five year survival: $\log\,[\theta/(1-\theta)] = 0.36969 - 2.38932P + 0.01917U + 1.60759T - 0.44481D + 1.83750S$, where θ = the probability of five year survival, P = pathological stage, U = ulceration, T = treatment, D = depth of invasion, and S = primary lesion site. The equation predicted an individual patient's probability of five year survival in close agreement with the observed numbers of five year survivals (Table 6). The close fit between the mathematical model and observed survival, and the discordance of factors found significant in the two types of statistical analysis strongly supports the superiority of regression analysis as a technique for more accurately identifying important prognostic variables.

Discussion

A multifactorial analysis is a powerful statistical method that minimizes selection bias, permits a more sophisticated examination of clinicopathologic correlates, and discriminates those factors that independently influence survival rates. Mathematical approaches such as this have been previously advocated to select different therapeutic strategies, such as selecting alternative surgical treatments and for identifying high risk patients as potential candidates for adjunctive

TABLE 3. *Melanoma Microstaging Five Year Disease-free Rate*§

Level of Invasion	Thickness (mm)					Total
	0–0.75	0.76–1.49	1.5–2.25	2.26–3.0	>3.0	
II	100% (55)*	69% (13)*				94% (68)
III	100% (16)†	65% (23)†	69% (13)	50% (8)	33% (5)	71% (65)
IV		66% (9)	68% (19)‡	11% (9)‡	25% (20)	43% (57)
V				100% (2)	15% (13)	27% (15)
Total	100% (71)	66% (45)	69% (32)	37% (19)	23% (38)	

§ The 205 patients at risk for recurrence five years or longer represent combined statistics from the University of Alabama Melanoma Registry and a previously published series[3] from the George Washington Medical Center. *p = 0.00002; †p = 0.008; ‡p = 0.005.

therapy trials.[7,20] Of the 13 variables compared simultaneously from our data, only five factors independently influenced survival of the entire population of melanoma patients: pathological stage, thickness, lesion ulceration, surgical treatment and anatomical location.

The pathological stage of disease was the most significant determinant of survival, as it reflected the localized, regionalized or distant extent of disease. The measured thickness of the primary melanoma was also an independent variable. It was the most important determinant of survival for Stage I patients, but had less predictive value for patients presenting with pathological Stage II and III disease. A multivariate analysis of 118 patients treated at the National Institutes of Health also showed that the number of metastatic regional nodes was the most important prognostic factor in pathologic Stage II disease and that the micro-

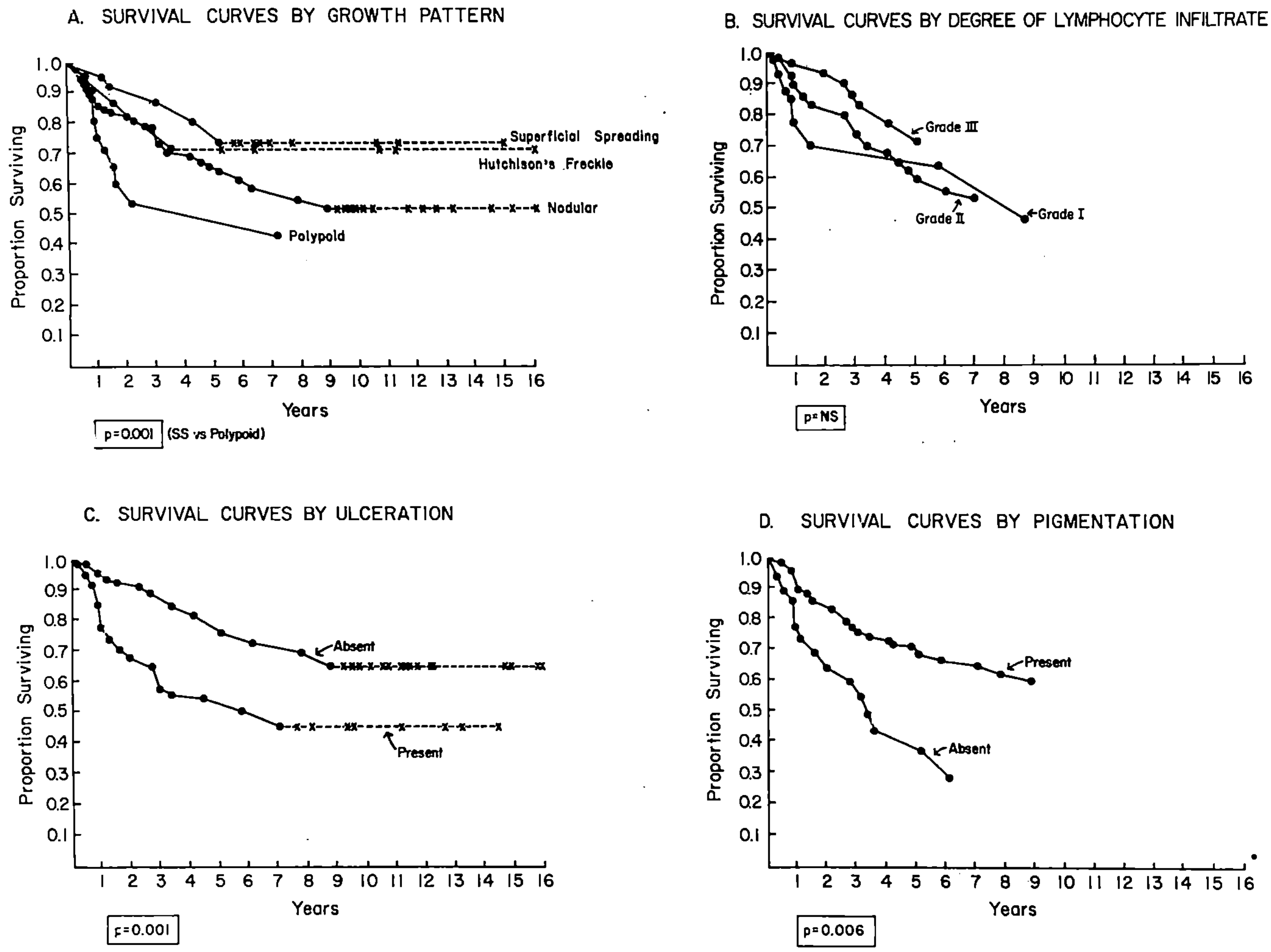


FIG. 4. Actuarial survival curves for four histopathological parameters of cutaneous melanoma.

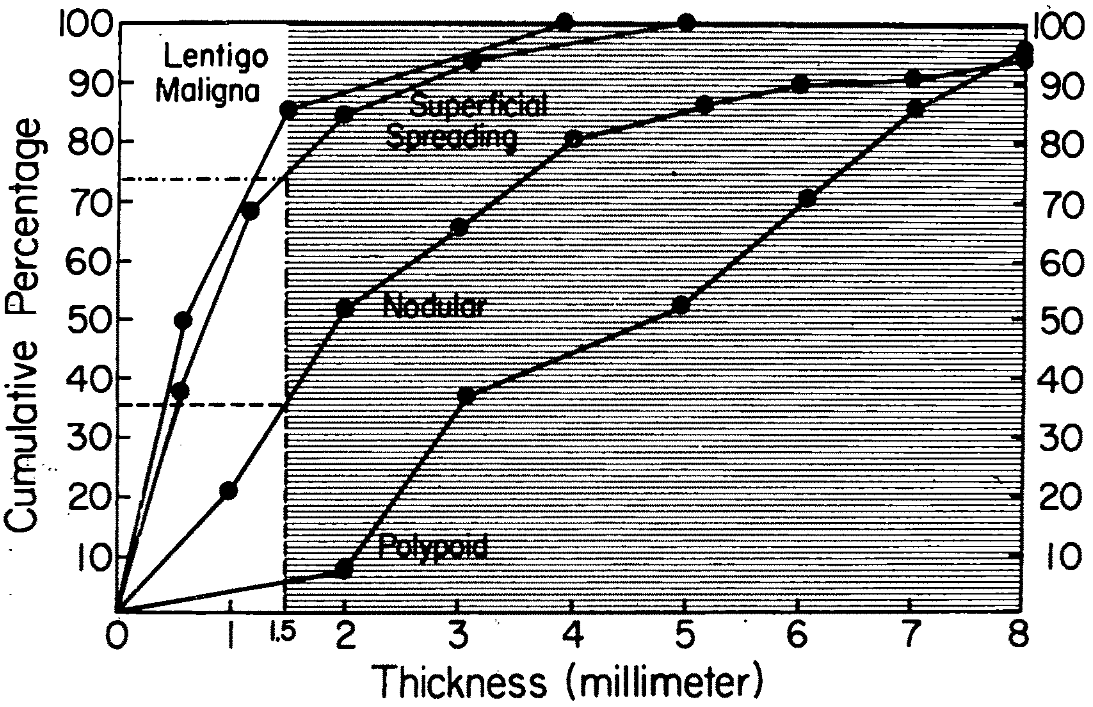


FIG. 5. Cumulative distribution of thickness measurements for each growth pattern.

staging of the primary melanoma was of prognostic importance only in patients with histologically negative nodes.[7]

In selecting optimal treatment alternatives for clinical Stage I melanoma patients, the measured thickness of melanoma invasion may be a valuable guide for identifying patients at risk for local, regional or distant disease. Thin melanomas with vertical dimensions less than 0.76 mm are localized in almost all cases, a finding that has been well documented in virtually all reported series. There is, therefore, no need for elective regional lymphadenectomy or systemic adjunctive therapies for such patients. Intermediate thickness lesions measuring between 0.76 and 4.0 mm have an increasing risk of harboring microscopic regional disease in draining lymph nodes, thus forming the rationale for performing elective regional lymphadenectomy in clinical Stage I patients. An improved survival rate with lymphadenectomy and a strong correlation of increasing melanoma thickness with greater risk of regional metastases has been well demonstrated in several series.[3,4,7,12,13,26] In our series, patients with melanoma of intermediate thickness (0.76–3.99 mm) had a statistically increased survival rate after elective node dissection, compared to those patients who had excision of the primary melanoma and subsequent lymphadenectomy for clinically apparent disease.[2] However, preliminary results of two randomized trials of elective lymphadenectomy for extremity melanomas have not demonstrated a statistically significant benefit after five years of follow-up.[21,25] Their results may become significant with a longer follow-up interval, since in our series the influence of lymphadenectomy was greatest at eight years or longer after surgery. Moreover, differences in study design and patient population between our study and the two randomized trials preclude any final judgment regarding the efficacy of elective lymphadenectomy but it appears from our data that there are subgroups of melanoma patients that benefit from this procedure.[2]

TABLE 4. *Single Factor Analysis of Melanoma (Single Variables Affecting Five Year Survival Rate Unaccounted for by Other Variables)*

Variables	p
Thickness	<0.00001
Pathological stage	0.00002
Clinical stage	0.0002
Clark's level	0.003
Ulceration	0.003
Pigmentation	0.025
Age	0.053
Growth pattern	0.231
Primary lesion site	0.354
Lymphocyte infiltration	0.438
Sex	0.479
Regression	0.590
Surgical treatment	0.638

The third risk category identified in our series was patients with thick melanomas exceeding 4 mm. These patients were at very high risk for harboring microscopic (or subclinical) distant metastatic disease at the time of initial diagnosis. The five year survival of 20% for patients with melanomas >4 mm in our series contrasts with that from the World Health Organization Melanoma Center whose patients with lesions exceeding 4.6 mm had a 50% or greater five year survival.[25] Their study, however, was restricted to extremity melanomas in a predominantly female population, while ours included all body sites, an equal number of males and females and a greater proportion of nodular melanomas, again stressing the need for multifactorial analysis in interpreting results.

Melanomas located on the upper extremity had a statistically better survival rate than melanomas in other locations. Trunk lesions had the worst prognosis of the four major groups analyzed, but this was not statistically significant. Most series have similarly reported that extremity melanomas fare better than trunk lesions.[7,15,22,24,31] The majority (79%) of our patients with extremity melanomas were females, whereas the majority (70%) of patients with trunk lesions were males. However, location, not sex was identified as the more important variable. The location of melanoma is thus an important factor to account for by stratification in clinical trials. Differences among clinical studies comparing alternative surgical treatments for clinical Stage I melanoma patients may have been significantly influenced by the mix of different melanoma thicknesses and anatomic locations between different treatment groups.

The presence of lesion ulceration as determined by microscopic evaluation correlated strongly with melanoma thickness (Table 2, $p = 0.0001$). Despite this, ulceration was an independent variable delineated by the multifactorial analysis. Thus, ulceration influenced survival within stage of disease (I vs II), thickness groups and types of surgical treatment.

The Clark's level of invasion significantly correlated with survival in the single factor analysis. However, the multifactorial analysis did not identify it as an independent variable. Its predictive value appeared generally to correlate with lesion thickness. However, there was some discordance that lessened its prognostic value. For example, patients with thicker Level II lesions, such as exophytic polypoid melanomas, generally fared poorly while those with thinner Level IV lesions had a relatively good prognosis especially when compared to survival associated with thicker Level IV lesions. Breslow[3] and Wanebo[26] have previously pointed out that tumor thickness and Clark's levels were congruent for Levels II and V, but not for Levels III and IV where there was wide variations in thickness and survival rates. Our data is exactly consonant with this view. On the other hand, survival rates for different thickness categories were unchanged when subgrouped by Clark's levels. These relationships were the same for our own analysis and from pooled data with Breslow's series (Table 3). Thus, it appears that the actual histological structures invaded by the melanoma are less predictive than the measured thickness. Moreover, others have reported that a microstaging technique using tumor thickness was easier than making assignments of Clark's level and was therefore more reproducible.[7,26]

TABLE 5. *Multifactorial Analysis of Melanoma (Dominant Variables Affecting Five Year Survival Rate after All Other Variables Have Been Accounted For)*

Variables	p
Pathological stage (I, II)	0.0014
Lesion ulceration	0.006
Surgical treatment	0.024
Thickness	0.032
Primary lesion site (upper extremity vs other)	0.038

TABLE 6. *Observed and Predicted Five Year Survivals From Logistic Regression Equation*

Predicted Probability of Five Year Survival	Total No. of Patients	No. of Five Year Survivals	
		Observed	Predicted
0–19%	18	1	1.4
20–39%	7	2	2.2
40–59%	11	7	5.7
60–79%	19	13	13.6
80–100%	42	38	38.1
Total	97	61	61.0

Other pathological factors also seemed to derive their prognostic value from the thickness of the primary melanoma. For example, lentigo maligna lesions on the face are generally regarded as highly curable melanomas. In our series, patients were cured if their lentigo maligna lesions were thin, but death occurred in two out of three patients with such melanomas of intermediate thickness. Polypoid melanomas were associated with a very poor prognosis but this association was also accounted for by their extreme thickness. Depigmentation was an adverse determinant of survival, but this was a secondary variable that correlated with thickness. Lymphocyte infiltration was not clearly associated with improved survival rate in this study despite the fact that thicker lesions were associated with a diminished host response. There was no correlation of survival with lesion regression in our series.

Microstaging using tumor thickness is thus an important factor for determining prognosis and guiding initial management of melanoma patients. It should be a critical aspect in any analysis of clinical trials concerning surgical treatment alternatives and adjunc-

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tive therapies. Our data distinguishes three subgroups of melanomas and relates the vertical dimension of their growth to subsequent biologic behavior. Thick melanomas (≥ 4.0 mm) were the most aggressive lesions. Pathologically, these lesions were associated with an increased incidence of ulceration, depigmentation and a diminished infiltration by host lymphocytes. Clinically, they were associated with a high risk of distant metastases. Converse relationships were observed for melanomas less than <0.76 mm in thickness. It is not clear biologically why melanoma thickness alone is a significant prognostic variable, especially when considering wide variations of skin thickness in different anatomic locations. Thicker lesions may represent more advanced melanomas and reflect an inherent biological aggressiveness of lesions with vertical growth as opposed to radial growth.[5]

The histopathological staging of melanomas provides important data relevant to clinical management. It, therefore, behooves the surgeon to consider carefully his biopsy techniques for suspicious pigmented lesions of the skin. Shave or curretted biopsies are contraindicated because they do not remove the entire lesion and thus compromise the accuracy of microstaging. An excisional or a punch biopsy that extends to the underlying subcutaneous tissues is essential.

Acknowledgments

Pathologists and clinicians throughout Alabama made an invaluable contribution to this analysis by sharing their pathology specimens of biopsy material and patient information for review. We thank Dr. Alexander Breslow, Department of Pathology, George Washington University Medical Center, Washington, D.C. for his comments and suggestions about the manuscript and for his permission to use some of his pathological data. We appreciate the encouragement and support for the Melanoma Registry by Dr. John R. Durant, Director of the Comprehensive Center, UAB. Skillful assistance was provided by Mr. Wayne Satterwhite in the data management, Ms. Enying Hsu in the statistical analysis and by Ms. Barbara Yarber, ART, in the preparation of this manuscript.

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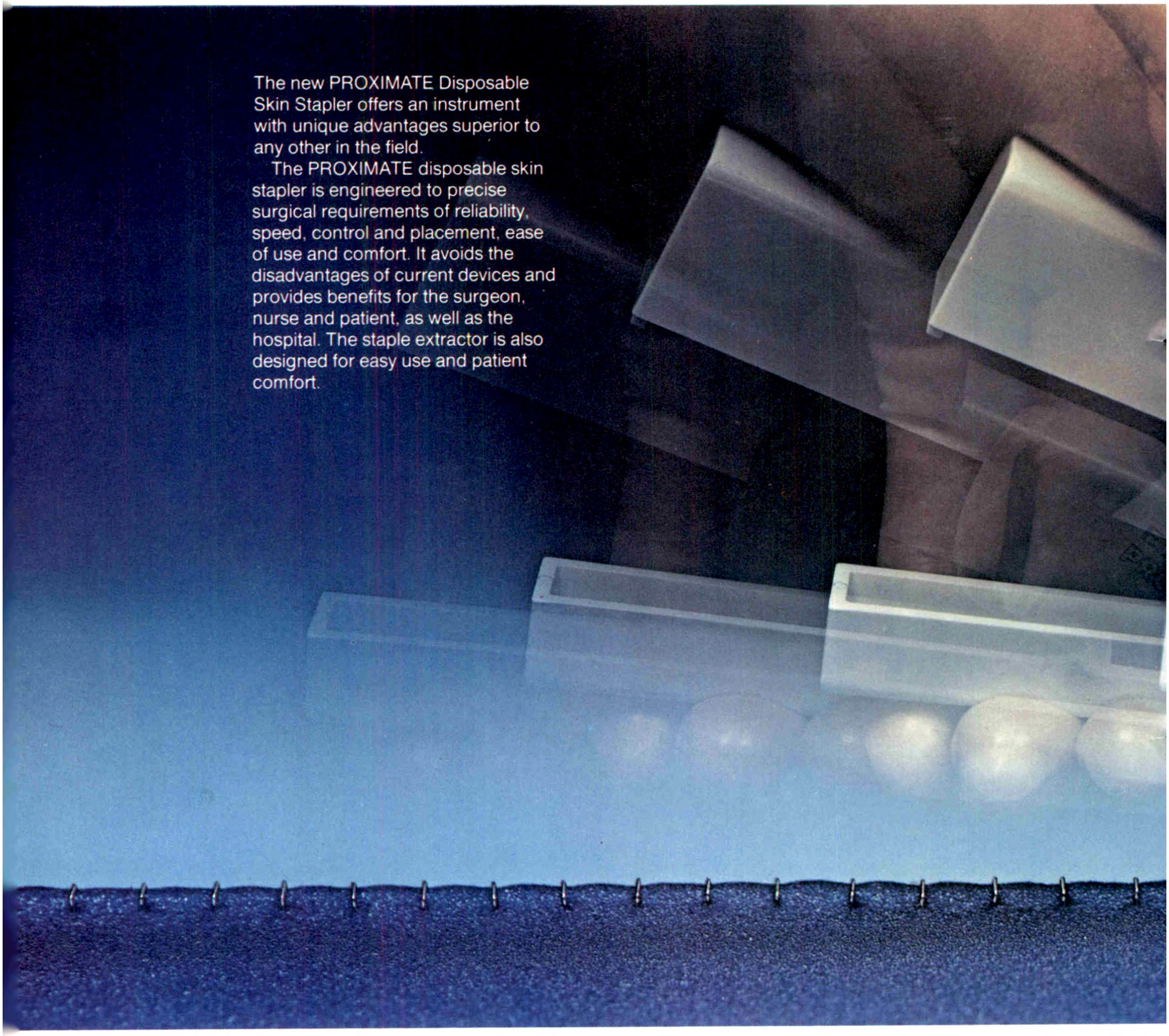

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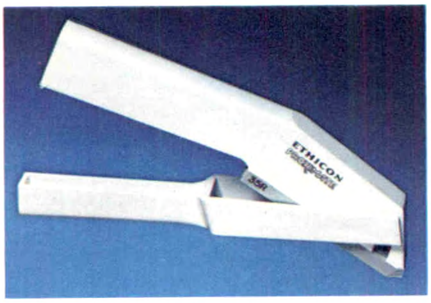

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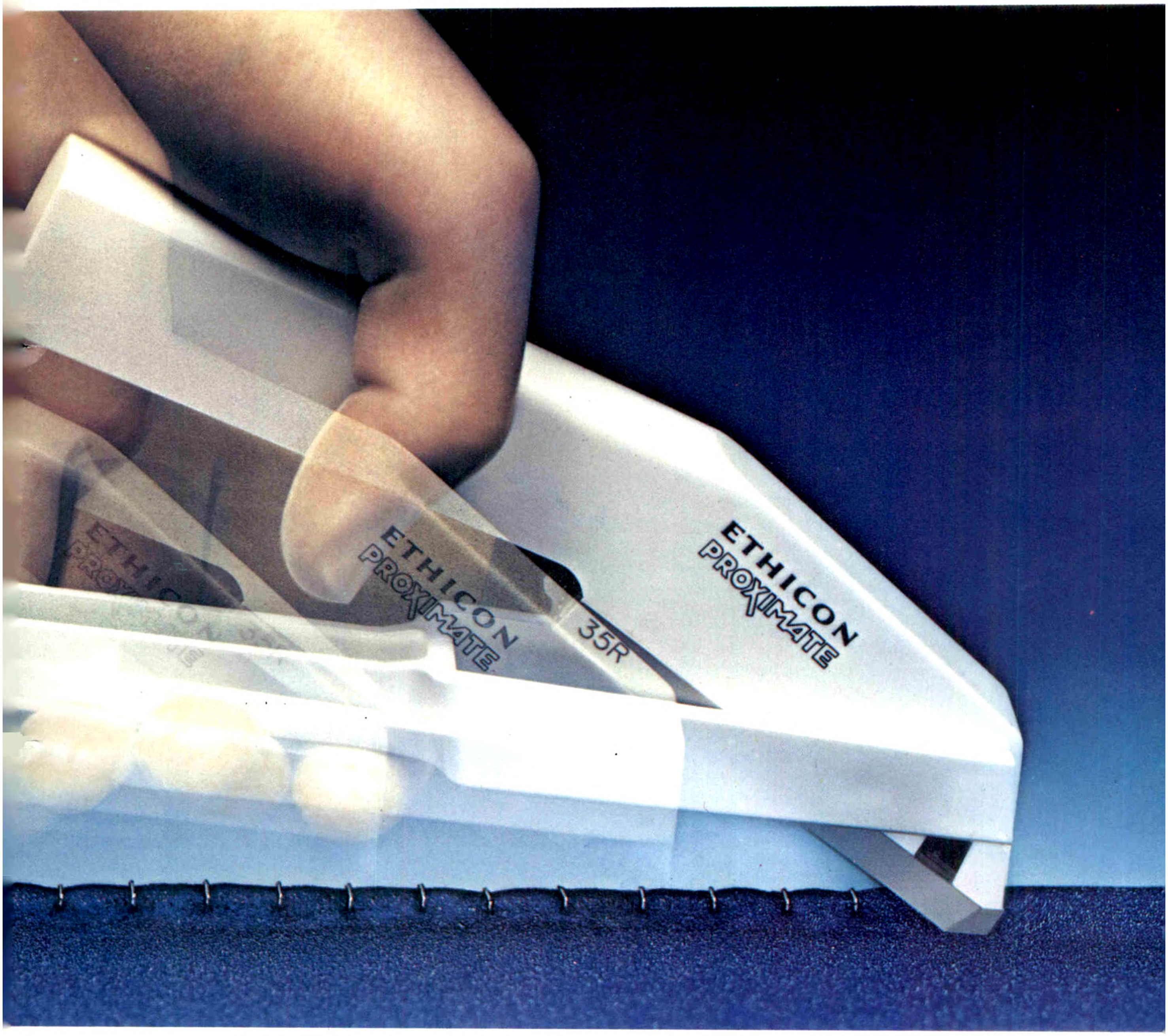

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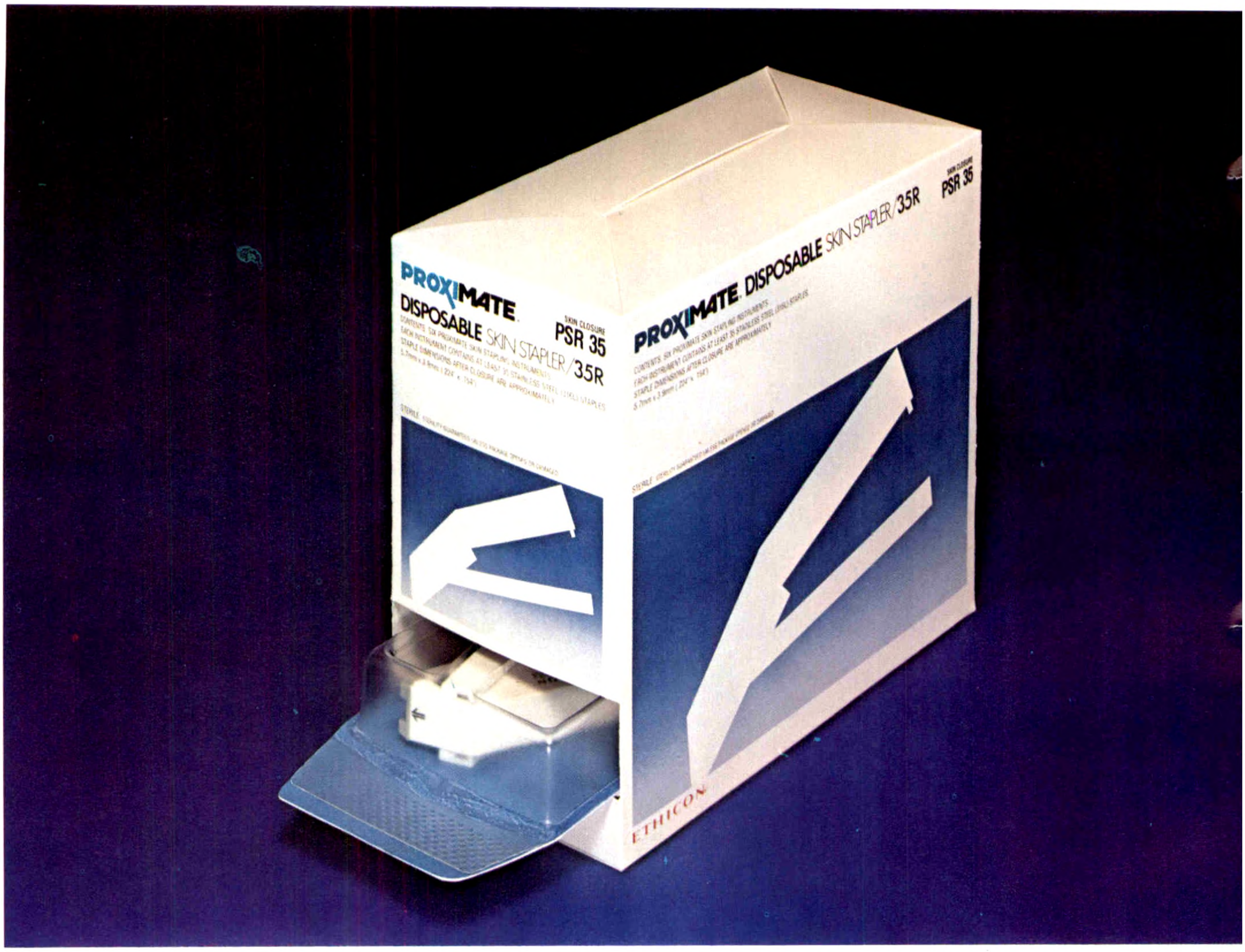

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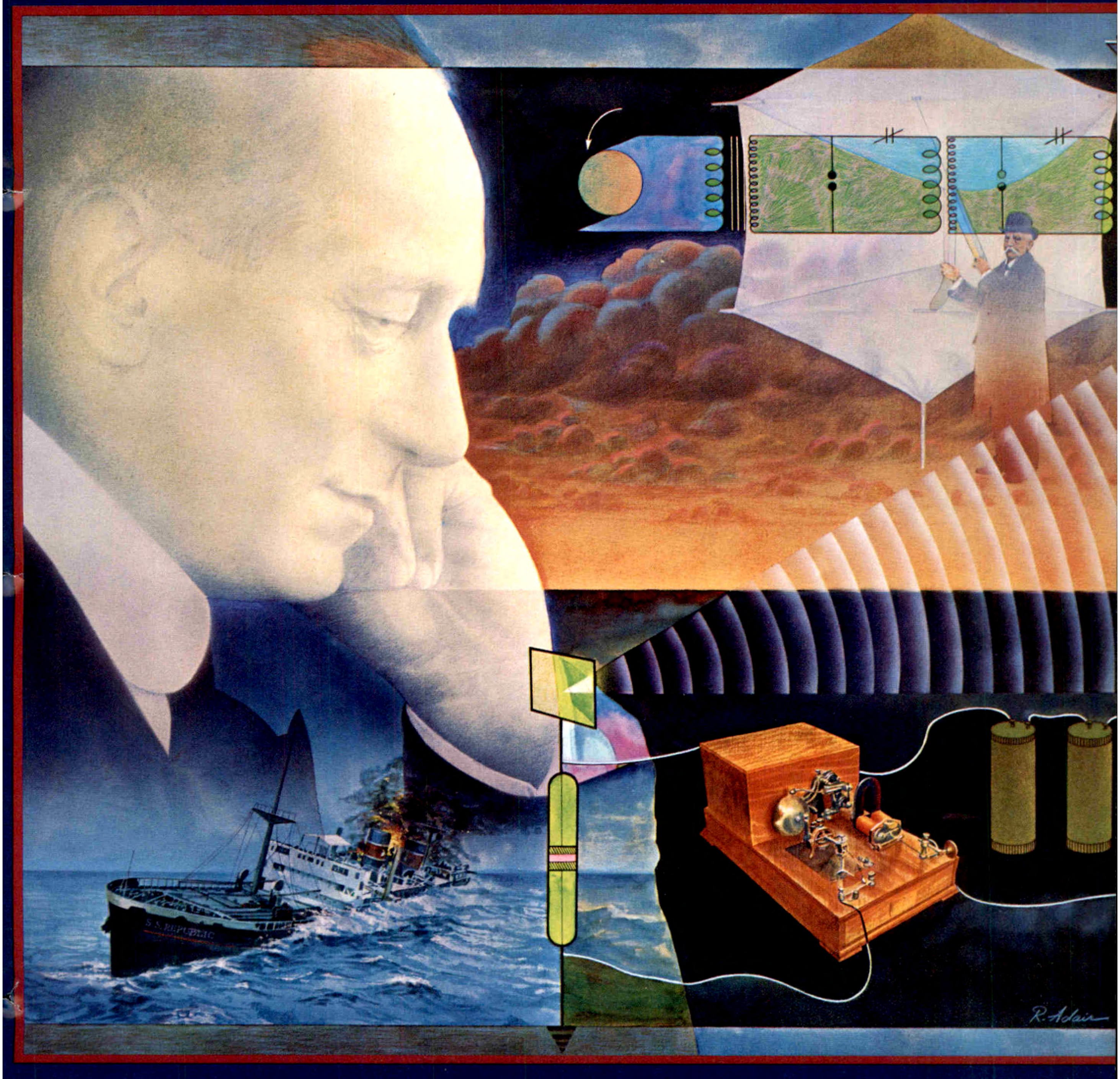

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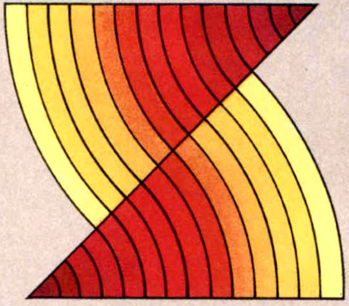

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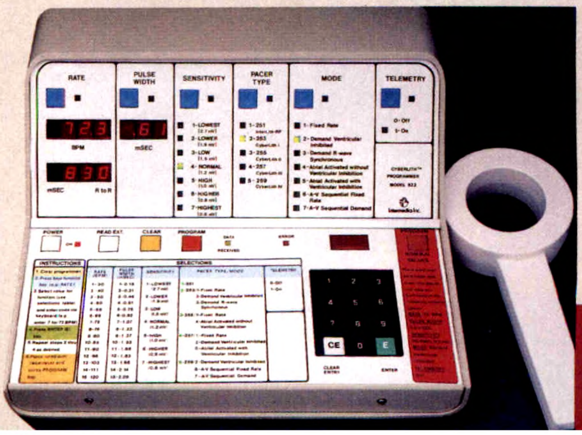

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1. Data on file, SK&F Medical Department. Tissue penetration is regarded as essential to therapeutic efficacy, but specific antibiotic tissue levels have not been directly correlated with specific therapeutic results.

For further information on contraindications, warnings, precautions and adverse reactions, see brief summary of prescribing information on next page.

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Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Urinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin structure infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci and other strains of streptococci.

Biliary tract infections due to *Escherichia coli,* various strains of streptococci, *Proteus mirabilis, Klebsiella* species and *Staphylococcus aureus.*

Bone and joint infections due to *Staphylococcus aureus.*

Genital infections (i.e., prostatitis, epididymitis) due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterococci.

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

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Contraindications: ANCEF (STERILE CEFAZOLIN SODIUM, SK&F) IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

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SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

Precautions: Prolonged use of 'Ancef' may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

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How Supplied: Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., or 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 500 mg. or 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

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A Prospective Randomized Study of Three Expanded Polytetrafluoroethylene (PTFE) Grafts as Small Arterial Substitutes

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A prospective, double-blind, randomized study was performed to determine the relative patency rate of polytetrafluoroethylene (PTFE) grafts, Gore-Tex,® Impra,® and a Surgikos® prototype PTFE graft. The 48 grafts (40 × 4 mm) replaced excised segments of femoral arteries in adult mongrel dogs, whose mean weight was 20.6 ± 0.9 kg; the grafts were removed after 12 weeks. Sterile technique and antibiotic therapy were included in the study. Anticoagulation was not employed. Anastomoses were performed with 6 = 0 polypropylene. Angiographic assessment of each anastomosis was made at surgery and prior to sacrifice. Patency was assessed daily by palpation and Doppler flow signals, as well as angiographically, prior to sacrifice. The overall patency rate was 62.5%. There were no statistically significant differences in patency rates among the three groups (Gore-Tex, 56%; Impra, 75%; Surgikos, 56%). Histologic evaluation revealed incomplete neointima formation and significant pannus formation in all three types of grafts without any significant discernible difference among them. The results suggest that further experimental evaluation of PTFE, as a small vessel substitute, is indicated prior to its use clinically in preference to autogenous vein.

EXPANDED POLYTETRAFLUOROETHYLENE (PTFE) was studied by Soyer[9] in 1972 as a large vein replacement in the piglet, with good results. The material was quickly adopted for study as a small arterial substitute. Matsumotu[5] reported an impressive patency of 100%, in a large series of dogs, using the graft as a femoral arterial implant. Unfortunately, the follow-up period varied and the details of the structural characteristics of the graft were not discussed in the report. In addition, nonporous Teflon® prostheses were used as controls and all of them were occluded between seven and 110 days postimplantation.

Campbell[2] compared graft fibril length and patency of prostheses placed in canine femoral arteries. He observed greater patency (88%) with relatively short ($<22\ \mu$) fibril length. Grafts with fibrils longer than 34 μ exhibited only 53% patency. The investigators included no control group and the postimplantation follow-up varied from three days to ten months in each group of animals.

Florian[3] studied the relationship between patency and PTFE fibril length of grafts used as small arterial and venous replacements in the dog. Surprisingly, 18 grafts having a fibril length of 100 μ were 100% patent in a postimplantation period which varied from two weeks to six months. Eighteen similarly observed grafts with fibril lengths of 10 μ were only 67% patent. There was no statistical analysis of the data presented.

The present study was performed to evaluate the relative patency at 12 weeks after implantation, handling characteristics, incidence of complications, histopathological features and structural characteristics of the two clinically available polytetrafluoroethylene grafts: Gore-Tex (W. L. Gore and Associates, Flagstaff, Arizona) and Impra (International Medical Prosthetics Research Associates, Phoenix, Arizona) with a polytetrafluoroethylene graft under development by Surgikos (A Johnson and Johnson Company, New Brunswick, New Jersey).

Materials and Methods

Four centimeter lengths of each of the three graft materials, each with an approximate diameter of 4 mm, were gas sterilized in coded packets. Physical properties of the graft materials are summarized in Table 1. Prior to surgery, each dog was assigned a

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Presented in part at the Fourth Annual Peripheral Vascular Surgery Seminar of the Society of Military Vascular Surgeons, Walter Reed Army Medical Center, Washington, D.C., December 1976.

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Submitted for publication: May 22, 1978.

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TABLE 1. *Summary of Physical Properties of the Three Graft Materials*

	Gore-Tex		Impra		Surgikos	
	$\bar{X}$	Std Dev	$\bar{X}$	Std Dev	$\bar{X}$	Std Dev
Internal diameter (mm)	3.76	0.08	4.11	0.07	3.21	0.18
Wall thickness	0.51	0	0.65	0.018	0.46	0.04
Fibril length	19.0	7.5	10.7	4.0	32.5	10.6

code number corresponding to a graft number. The investigators did not have access to the graft identification code until the time that the grafts were excised. Questionnaire forms were provided to the operating surgeon following the implantation of each prosthesis, identified by its code number. Each investigator reported his opinion of the strength of the graft, ease of handling, postimplantation bleeding and conformation of the prosthesis to the femoral artery.

Twenty-four, adult, mongrel dogs were anesthetized with intravenous pentobarbital (Nembutal, 20 mg kg^{-1}), intubated and mechanically ventilated with room air. The groin areas were shaved, sterily prepared with povidone-iodine (Betadine®) and draped. Penicillin was administered intravenously in doses of 500,000 U, and 0.5 gm of streptomycin was given intramuscularly, 60 minutes prior to surgery.

A segment of femoral artery, approximately 6 cm long, was isolated between vascular clamps. No anticoagulants were administered either systemically or locally, pre- per- or postoperatively. The arteries were transsected and a 2 cm segment was excised to permit implantation of the prosthesis without redundancy or excessive suture line tension. Standard end-to-end anastomoses were performed using continuous 6-0 polypropylene sutures (Ethiflex, Ethicon, Somerville, New Jersey). A representative graft is shown in Figure 1. Arrows point to proximal and distal arterial segments.

After the vascular clamps were removed, there was relatively vigorous bleeding from the needle holes in all the grafts. Hemostasis required gentle digital pressure with a dry sponge for up to 15 minutes.

An operative angiogram was then performed by injection of 10 ml sodium diatrizoate (Renografin 60, E. R. Squibb & Sons, New York, New York) through the proximal common femoral artery, using a No. 21 gauge needle. A typical arteriogram is shown in Figure 2. If no evidence of technical error or early graft thrombosis was detected on arteriogram, the incisions

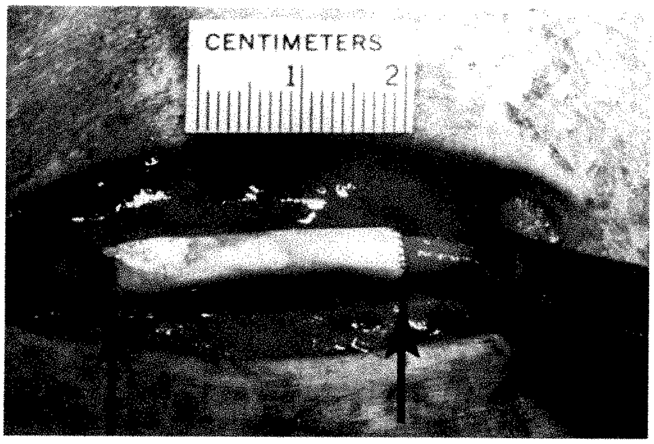

FIG. 1. The typical appearance of a freshly implanted PTFE graft. Arrows point to proximal and distal arterial segments.

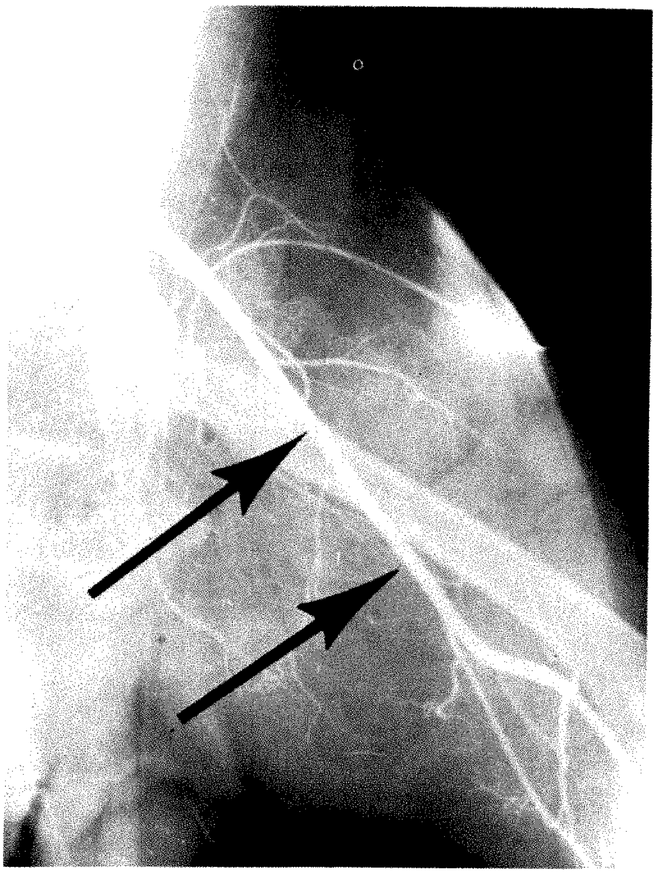

FIG. 2. A typical operative arteriogram showing a patent graft and no technical errors in the suture lines (arrows).

were closed in layers using absorbable suture material. After the administration of 5% dextrose in Ringer's lactate, 1000 ml, and a second identical dose of antibiotics, the animals were returned to their cages.

The animals were evaluated by inspection and palpation of the graft, daily, for a period of 12 weeks. The Doppler flowmeter® (Parks Electronics, Beaverton, Oregon) was also employed. The presence or absence of a graft pulse was recorded. Disappearance of palpable, or audible, graft pulse was regarded as presumptive evidence of graft occlusion. Absence of a pulse, within 48 hours of operation, was regarded as a technical failure and the graft was excluded from the study.

Twelve weeks after implantation, the animals were reanesthetized and the grafts were surgically exposed. An arteriogram was performed and the grafts were removed. The grafts were opened longitudinally; the lumen was examined and photographed. Sections of each graft were mounted in parrafin blocks, sectioned and stained with hematoxylin and eosin and examined by a pathologist who was not aware of the manufacturer identity of the coded specimens.

Data from questionnaire forms completed at the time of the operation were analyzed for variance, and statistical significance of apparent differences assessed with Student's t-test for paired observations. Patency data were evaluated with the chi-squared method of statistical analysis.[8]

TABLE 2. *Summary of the Patency and the Histology of the Three Graft Materials at the End of 12 Weeks*

	Gore-Tex	Impra	Surgikos
Patent	56% (7/16)	75% (12/16)	56% (7/16)
Mural thrombus	53%	31%	43%
Pannus	47%	56%	50%
Neointima* formation	29%	31%	21%

* Estimated percentage of graft wall with a formed neointimal cell layer.

Results

The combined patency of the three grafts was 62.5%. There were no significant differences ($p > 0.05$) in patency among the three materials (Gore-Tex 56%, Impra 75%, Surgikos 56%). The histologic observations and numbers of occluded grafts for each type of material are summarized in Table 2. In general, all three types of grafts showed a large amount of pannus formation (Fig. 3) and incomplete neointimization (Fig. 4).

There were two technical errors found in the study, a redundant graft, as demonstrated on a postoperative arteriogram (Fig. 5), and one occluded graft in less than 24 hours after surgery. Both grafts were excluded from the study. There were two complications: 1) One wound infection occurred within three days of surgery and resulted in fatal sepsis, despite continuous antibiotic therapy, fluid support and adequate drain-

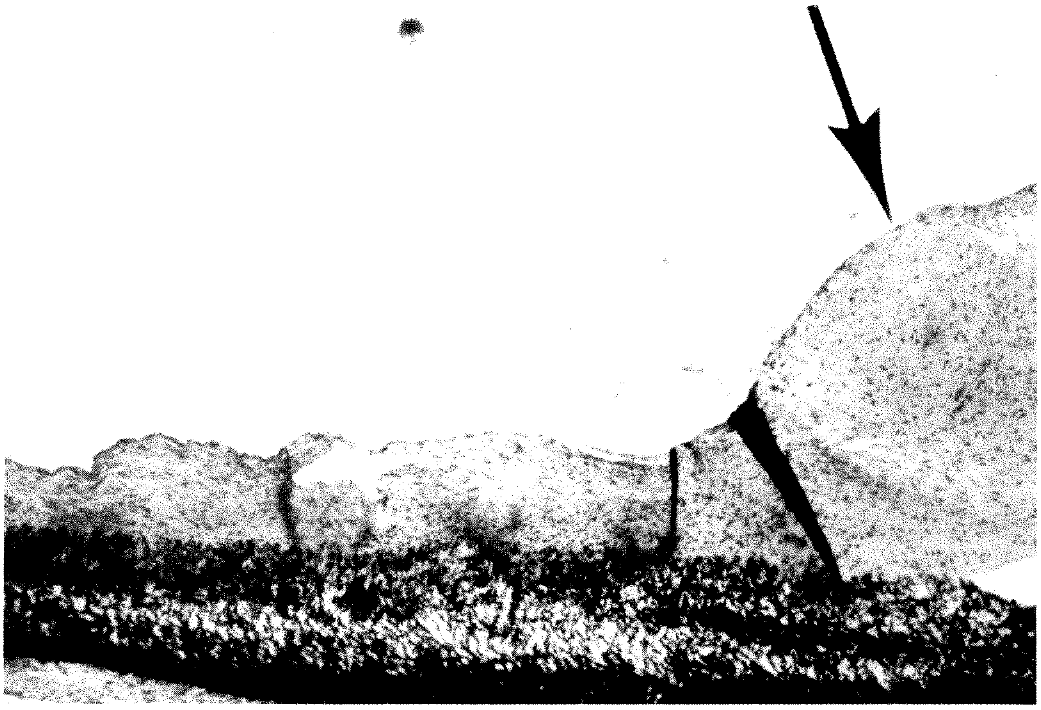

FIG. 3. A cross section of a PTFE graft near the anastomosis showing pannus formation—H and E low power. Arrow points to graft inner wall and pannus.

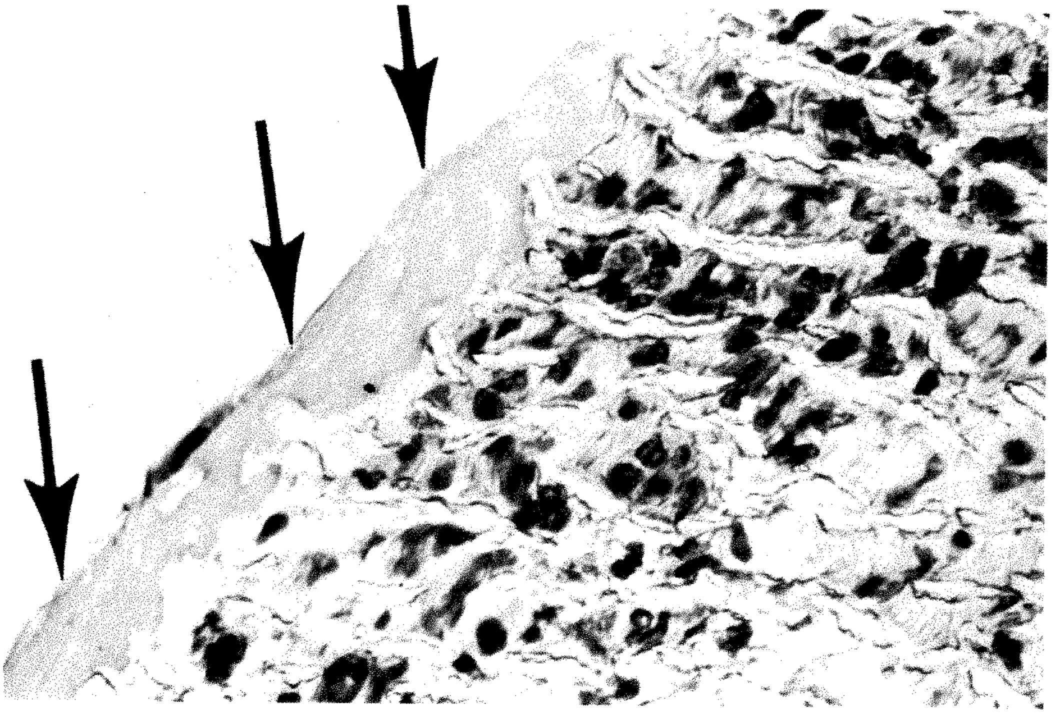

FIG. 4. Cross section of a typical PTFE graft, (removed after a 12 week implantation) which does show a neointimal layer, but an area of fibrin deposition (arrows)—H and E high power.

age. 2) An aneurysm developed in one Impra graft, as demonstrated on the pre-sacrifice arteriogram (Fig. 6).

Discussion

Teflon is a biologically inert, fluorinated hydrocarbon polymer, which is hydrophobic and bears an electrically negative surface change. A process of stretching and heating Teflon produces a porous material composed of nodes connected by thin fibrils. Variations in the "stretching" procedure produce a material of varying porosity or fibril length. The porosity of the material varies directly with fibril

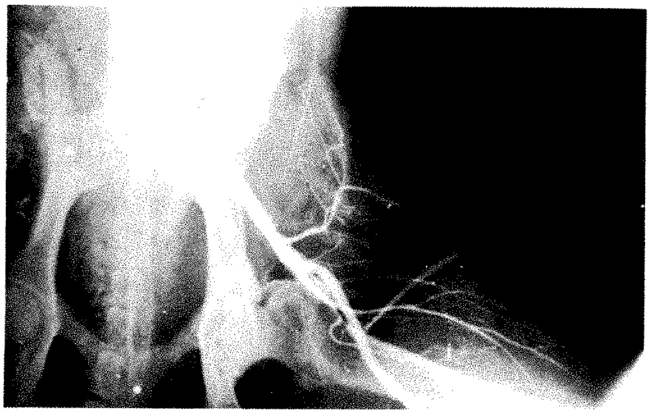

FIG. 5. Postoperative arteriogram demonstrating the redundant graft, which was removed from the study.

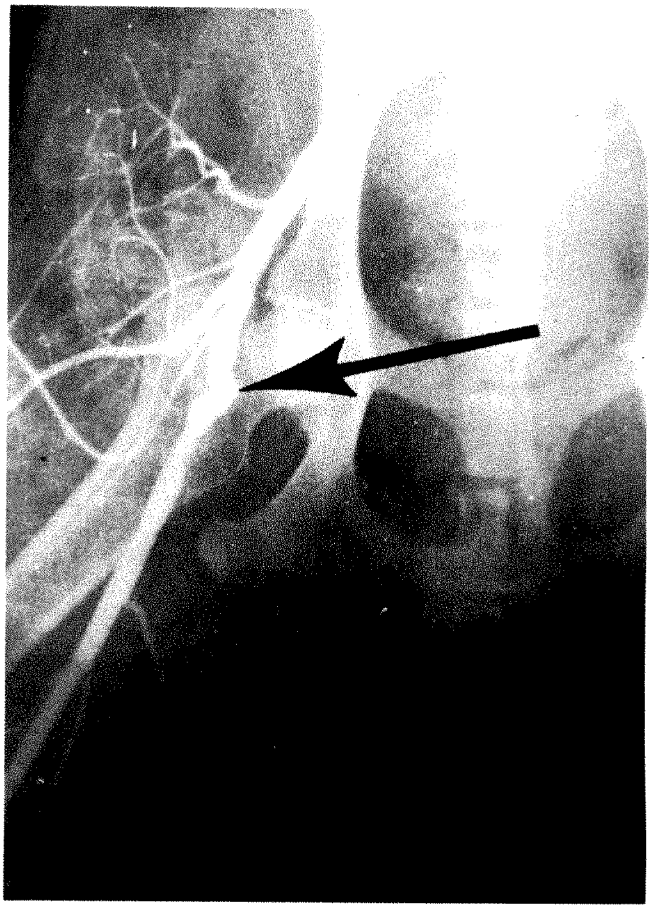

FIG. 6. The arteriogram of an Impra graft, 12 weeks after implantation, showing a true aneurysm of the prosthesis (arrow).

length. It is through these open spaces that connective tissue ingrowth and capillary formation occur.

These features make PTFE an exciting material, on a theoretical basis, for use as an arterial substitute. However, the difficulties in handling the currently available grafts, as well as their incidence of thrombosis in our initial experience with the material, suggests that clinical use must await further improvement in polytetrafluoroethylene as a small vessel substitute. Sauvage[7] reported that certain PTFE grafts were thrombogenic, and the inner walls of grafts studied by Smith[7] were coated with thrombus soon after implantation in the canine aorta. Unfortunately, this work was not published, and the structure of the graft studied was not disclosed.

It is also important to recall that, as reported by Sauvage,[7] the healing of a vascular prosthesis occurs at a much slower rate in man than in lower animals. Therefore, excellent results in animal experiments may not be duplicated in clinical studies.

These grafts were reported to form complete neointimal layers in the experimental studies already cited by Campbell, Florian and Matsumoto. The results of this study clearly show a lower combined patency than the other reported studies using PTFE grafts as canine femoral arterial replacements.

Campbell[1] has reported the use of 30 μ (fibril length) grafts manufactured by Gore-Tex for limb salvage procedures in 15 patients who did not have autologous saphenous vein available. Among this group of patients, 13 out of 15 grafts, or 87%, were patent at varied postoperative intervals (one to eight months). In an addendum to the clinical report, four grafts of 50, performed over an extended period, formed true aneurysms. Three of four of the patients were hypertensive. In response to this problem, the Gore-Tex grafts have been wrapped with an outer jacket of PTFE for additional wall strength.

Johnson[4] reported clinical experiences with the graft as an arterial substitute in femoral popliteal and distal bypass procedures, in 15 patients. There was one graft which occluded and the patient did not require amputation. Another graft thrombosed and was treated by a simple thrombectomy. One patient developed a groin hematoma, which required surgical drainage. No aneurysmal formation was reported; the average followup period was nine months. It is interesting to note that the only aneurysm in our series occurred in an Impra graft.

Although these clinical reports are encouraging, there have been too few cases performed with too short follow-up periods to ascertain the clinical efficacy and safety of this material, in the present configurations. For widespread clinical use of these grafts for small arterial reconstructive surgery, caution should be exercised.

We conclude that the best structure of the grafts for optimum patency has not been determined. The material is certainly inferior to autologous vein grafts in dogs, since patency rates of 87%, at 49–72 weeks after implantation, have been reported by Perloff.[6] We suggest that further work be done to obtain a better graft structure in experimental animal models. We do not advise routine clinical use of these grafts in the community hospital setting and suggest that prospective and randomized clinical studies be reported from the centers already using the grafts.

In a recent regional meeting of vascular surgeons* several investigators reported that they were using Gore-Tex in preference to available autogenous saphenous vein. In view of our findings, we feel that this position is unwarranted and urge our colleagues to continue use of autologous vein whenever it is available, for small arterial reconstructive surgery.

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* Sponsored by W. L. Gore and Associates, Plaza Hotel, New York, New York, June 1977.

Carotid Endarterectomy:

A Follow-up Study of the Contralateral Non-operated Carotid Artery

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JAMES J. GOODREAU, M.D., JAMES S. T. YAO, M.D., PH.D., JOHN J. BERGAN, M.D.

In a study of 103 patients surviving carotid endarterectomy, follow-up information was obtained from all patients over a period of time extending to four years. This was done so that better decisions could be made regarding recommendations for contralateral carotid surgery. In this follow-up study, only three patients had contralateral surgery. Three additional patients had events clearly in the territory supplied by the contralateral carotid artery, and no patient suffered a contralateral stroke. There were an additional four patients who suffered stroke in territory not supplied by the contralateral carotid artery. In addition, four patients experienced classical transient ischemic episodes referrable to the operated carotid artery and ten patients experienced nonclassical cerebral ischemia. Seven of the 103 patients died at times remote from the carotid surgery of nonstroke cause.

From the Division of Vascular Surgery of the Department of Surgery, Northwestern University Medical School, Chicago, Illinois

CAROTID ENDARTERECTOMY is an important therapeutic modality in the treatment of extracranial cerebrovascular insufficiency. Because carotid artery lesions are frequently bilateral, decisions must be made regarding management of the non-operated, frequently severe, contralateral lesion. Suggestions for such therapy range from studious neglect to simultaneous bilateral carotid endarterectomy,[3] and include frequent suggestions for staged bilateral carotid reconstruction.[11]

Cerebral ischemic symptoms are frequent following carotid endarterectomy and may occur at any time in the early or remote postoperative period. The Joint Study of Extracranial Arterial Occlusion[5] reported that 38% of patients surgically treated had recurrent transient ischemic episodes during the follow-up period. Neary all of these episodes were noncarotid territory events but 3.8% affected the area perfused by the reconstructed artery. This and other studies have not made clear what can be expected from a carotid lesion contralateral to one surgically corrected.

The purpose of this study was to obtain concrete information relative to the natural history of the non-operated carotid artery so that better decisions could be made regarding patient care in the future.

Patient Population

This study is concerned with the follow-up evaluation of 103 consecutively treated patients who survived carotid endarterectomy. No patients were excluded from the study for any reason. Evaluation was directed specifically toward determining the presence or absence of classical transient ischemic attacks and stroke events. In addition, a search was made for nonclassical ischemic episodes.

Characteristic transient ischemic attacks were defined as unilateral paresis, paralysis, numbness or other paresthesias of face, arm or leg, with or without contralateral visual field quadrantanopsia, hemianopsia or blurring. Scotomata or amblyopia, when present, with or without speech difficulties of any kind, were also noted.

Clinical characteristics of nonclassical transient ischemic episodes included vertigo, diplopia, ataxia, dysthesias, unsteadiness, bilateral paresthesias or frank drop attacks.

Following carotid endarterectomy, patients were routinely evaluated at two weeks, six weeks, three months, and then followed at six month intervals. In this group of 103 patients, the average length of follow-up was 24 months with a range of six to 42 months. Patients dying at times remote from the carotid endarterectomy were included in the study and the cause of death determined from hospital

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Supported in part by the Dr. Scholl Foundation and the Northwestern University Vascular Research Fund.
Submitted for publication: May 11, 1978.

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TABLE 1. *Deaths*

Death No.	Age	Sex	Time from Operation	Cause of Death
1	59	M	8 months	Dissecting thoracic aneurysm
2	68	M	16 months	Myocardial infarction
3	69	M	24 months	Metastatic cancer of the lung
4	75	M	4 months	Myocardial infarction
5	50	M	21 months	Myocardial infarction (probable)
6	59	M	15 months	Suicide
7	72	M	29 months	Myocardial infarction (probable)

records, autopsy reports or death certificates. Follow-up of patients was 100% complete.

Mortality

Of the 103 patients surviving carotid surgery and subsequently discharged from the hospital, seven died at various times remote from the surgical event. The cause of death is listed in Table 1. As indicated in Table 1, none of the patients dying subsequent to carotid endarterectomy actually died from stroke of the ipsilateral or contralateral cerebral hemisphere. Apart from suicide and metastatic carcinoma, cardiac vascular lesions were the most important determining factor in whether or not a patient survived long-term following carotid endarterectomy.

Neurologic Events

Table 2 indicates the subsequent neurologic state of patients ranked according to whether the contralateral carotid lesion was greater or less than 50% narrowed. As indicated, there were 13 patients with complete occlusion of the contralateral carotid artery, just as there were 13 with less than 10% narrowing of the vessel. There were 22 patients with patent carotid arteries which were more than 50% narrowed, 11 with 31–50% narrowing, and 44 with 11–30% narrowing of the vessel.

Following successful carotid endarterectomy, no patient had a full stroke affecting the contralateral cerebral hemisphere. Three patients had symptomatology ipsilateral in the hemisphere affected by carotid endarterectomy, and one patient with less than 10% narrowing had a brain stem stroke.

Classic transient ischemic attacks were present in four patients. Three of these were confined to the contralateral cerebral hemisphere while one affected the cerebral hemisphere on the operated side.

There were a total of ten patients with nonclassical cerebral ischemic episodes. These were evenly dispersed across the population of patients with or without contralateral internal carotid occlusive disease. In addition, there were three patients who were subjected to contralateral carotid endarterectomy (Table 3). As indicated in Table 3, one patient was found to have total occlusion of the internal carotid artery at the time of surgery. This occlusion had not been identified at the time of angiography. The internal carotid artery could not be opened and external carotid endarterectomy was done. The patient continued to have symptoms of dizziness and these were relieved by the second carotid endarterectomy. A second patient had his first carotid endarterectomy on the basis of symptoms and in an artery narrowed 50%. The contralateral artery was narrowed 90% and a second carotid endarterectomy was done electively. The third patient requiring further surgery was asymptomatic for 18 months, developed amaurosis fugax in the carotid territory not operated upon, and was subjected to a secondary procedure.

It should be noted that 74 of the 103 patients (or 74 of 95 at-risk patients) were totally asymptomatic. Ten of these had complete contralateral carotid occlusion. Fifteen had stenosis greater than 50% on the contralateral side. Despite this, they remained asymptomatic.

TABLE 2. *Postendarterectomy Neurologic Status*

Occlusion of Contralateral Carotid	Greater than 50%		Less than 50%			
	Complete	51–99%	31–50%	11–30%	0–10%	Total
Strokes						
Contralateral to surgery	0	0	0	0	0	0
Ipsilateral to surgery	0	0	0	3	0	3
Brain stem	0	0	0	0	1	1
Classic T.I.A.'s						
Contralateral	0	2	0	1	0	3
Ipsilateral	0	0	0	1	0	1
Nonclassic T.I.A.'s	2	1	1	3	3	10
Bilateral endarterectomies	1	1	0	1	0	3
Deaths	1	2	1	3	0	7
Asymptomatic	9	16	9	32	9	75
Total	13	22	11	44	13	103

TABLE 3. *Indications for Staged Bilateral Carotid Endarterectomy*

Case No.	Stenosis Right	 Left	Interval between Operations	Indication
1	100%*	50%	6 weeks	Continual symptoms (dizziness)
2	90%	50%†	6 weeks	Prophylaxis (stenosis)
3	10%	10%	18 months	Amaurosis fugax

* At operation discovered to have complete occlusion, an external carotid endarterectomy was done. †The lesion which was symptomatic was operated upon first.

Table 4 displays a compilation of causes of stroke in those patients suffering from this event at times remote from carotid artery surgery. Patient 9 developed right lower extremity monoparesis and dysphasia during angiography and the stroke should be ascribed to that event. The cerebral hemisphere affected was that operated upon. Patient 10 experienced right hemiparesis. Thus, in these two patients, it is unlikely that the non-operated carotid artery was the cause of the cerebral event. Patient 11 experienced amaurosis affecting the eye contralateral to carotid surgery. Reangiography showed thrombosis of the posterior cerebral artery on the side ipsilateral to the carotid endarterectomy. Patient 12 developed nonlateralizing dizziness and ataxia which improved gradually. It should be noted that each of these four patients had contralateral internal carotid stenosis of less than 10% severity.

Transient ischemic episodes as differentiated from full strokes are also important after carotid endarterectomy. There were 14 patients who had such events. One had an event confined to the territory supplied by the operated artery. Three had such events confined to the territory of the non-operated carotid artery and ten patients had nonlateralizing findings. Table 5 displays these patients and indicates their symptomatology in some detail.

Effect of Contralateral Carotid Stenosis upon Symptomatology

In the 35 patients who had contralateral carotid stenosis greater than 50%, 13 had complete occlusion of the contralateral artery. Nine of these patients have been asymptomatic while two have nonlateralizing and nonclassical transient ischemic episodes. No patient in this group has suffered a stroke. One patient had an attempted bilateral carotid endarterectomy. One of the 13 patients with contralateral total carotid artery occlusion died of a dissecting thoracic aneurysm.

In the 22 patients with contralateral carotid stenosis ranging from 50 to 99%, three have had transient ischemic attacks. Two of these have been classical contralateral transient ischemic attacks and one has been nonclassical. None of the patients in this group of 22 has had a stroke but there have been two deaths. These were due to myocardial infarction and carcinoma. Sixteen of the 22 patients are totally asymptomatic and have been so since the carotid artery surgery. One patient has required staged bilateral carotid endarterectomy because of severe stenosis of the non-operated artery.

Sixty-eight of the 103 patients had contralateral carotid artery stenosis of less than 50% narrowing. The 11 patients with stenosis ranging from 30 to 50% severity have suffered no strokes and there

TABLE 4. *Causes of Stroke Remote from Carotid Artery Surgery*

Case No.	Age	Sex	Contralateral Stenosis	Operated Side	Time from Operation	Warning Symptoms	Signs and Symptoms
9	71	F	10%	L	10 months	TIA Expressive aphasia, right arm weakness	At time of transfemoral cerebral angiography, developed right hemiparesis and aphasia.
10	47	F	10%	L	1 month	None	Right hemiparesis and aphasia. Angiogram interpreted as showing normal postoperative changes with normal intracerebral vessels.
11	63	F	10%	L	7 months	Amaurosis fugax, right eye	Blindness of right eye. Angiogram demonstrated thrombosis of left posterior cerebral artery.
12	71	F	<10%	L	18 months	None	Dizziness, vertigo and ataxia. Gradually improved over 2 weeks.

TABLE 5. *T.I.A.'s Occurring after Carotid Endarterectomy*

Case No.	Age	Sex	Contralateral Stenosis	Operated Side	Recurrent Symptoms
14	65	M	60%	R	Amaurosis fugax O.S.
15	70	M	60%	L	Right arm and leg weakness lasting 10 minutes
17	57	M	10%	L	Amaurosis fugax O.D.
18	65	F	20%	L	Right arm numbness and weakness
19	60	F	100%	L	Feels "light-headed and woozy," also diagnosed as hysterical neurosis, conversion
20	57	M	100%	L	Bilateral episodes of "dim vision" lasting 5 seconds
21	75	M	60%	L	Episodes of light-headedness and unsteadiness
22	73	F	30%	R	Episodes of light-headedness and unsteadiness
24	70	F	20%	R	Syncope and dizziness
25	55	M	10%	L	Light-headedness and unsteadiness
26	55	F	10%	L	Occasional unsteadiness
27	57	M	<10%	R	Two episodes of bilateral blurring of vision lasting 10 minutes
28	63	M	<10%	L	Episodes of dizziness lasting ±30 minutes of 3 to 4 months duration
29	62	M	<10%	L	Dizzy spells lasting ±30 minutes

have been no deaths. One of these developed nonclassical transient ischemic episodes and the remaining are asymptomatic. There were 44 patients with contralateral lesions ranging from 10 to 30% in severity. Three of these patients had ipsilateral strokes, one of which occurred at the time of transfemoral cerebral angiography. Six developed transient ischemic attacks. One of these was a classical contralateral transient ischemic episode; one was a classic ipsilateral transient ischemic attack; and four had nonclassical episodes. Three of these 44 patients died, none of cerebrovascular event, and one patient had a subsequent contralateral carotid endarterectomy because of amaurosis fugax. Thirty-two of the patients have remained symptom-free since surgery.

Thirteen patients had a contralateral lesion less than 10% occlusive. Despite this, three patients developed nonclassical transient ischemic attacks and there were none with classic transient ischemic attacks. One patient of the 13 suffered a brain stem infarct and there was one death from myocardial infarction.

Study Summary

In this group of 103 patients surviving carotid endarterectomy, seven died remotely of nonstroke cause, four sustained a stroke, four experienced classical transient ischemic attacks, ten experienced nonclassical cerebral ischemia, and three additional patients were subjected to staged bilateral carotid surgery. Thus, only three patients had contralateral surgery, three had events clearly in the territory supplied by the contralateral artery, and no patient suffered a contralateral stroke.

Discussion

The natural history of patients having transient ischemic attacks from a carotid lesion is well known. In six studies describing a total of 426 patients, the natural history of transient ischemic attacks was reported.[1,5-9] Recurrent attacks occurred in 24% of patients (range 17–47%), and an additional 26% (range 7–47%) developed frank stroke. Mortality of these patients averaged 21% (range 17–32%) during the follow-up period. Thus, transient ischemic attacks as a symptom are clearly a severe warning of incipient stroke or, at best, continuation of symptoms.

Of some pertinence is the fate of patients surviving carotid endarterectomy. While the risk of death within 30 days of the surgical event is very low, the risk of death within five years of the operation is very high. DeWeese, et al.[4] reported 34 of 103 patients dying within five years; Toole[12] et al. reported 23% of their patients dying within four years; Siekert, et al.[9] reported 44 of 160 patients dying during 60 months of follow-up; and Fields[5] reported 26 deaths in 145 patients followed 42 months. This mortality is not unexpected, as it is comparable to the mortality reported by Boyd,[2] who followed 1,476 patients with intermittent claudication of the lower extremities and found that 28% died within five years. With this impaired prognosis in mind, it is extremely important to select very carefully those patients for a second carotid endarterectomy.

DeWeese,[4] reporting on 103 patients with carotid endarterectomy for transient ischemic attacks, noted that 24 of the 103 patients developed new neurological symptoms; 13 of these patients had classical transient ischemic attacks while 11 suffered completed strokes compatible with other lesions of extracranial vessels. In that series of patients followed more than five years, 17 patients underwent contralateral endarterectomy, 12 of which were for symptomatic lesions and five were prophylactic.

Thompson[11] has called attention to the fact that patients who have undergone successful carotid endarterectomy are quite different from those who have a carotid lesion and have not undergone carotid surgery. He has pointed out that the latter group of patients having an asymptomatic carotid lesion pose a different problem than the former group of patients having one successfully repaired carotid artery. He recommended staged repair for severe bilateral lesions "that pose a threat of early thrombosis" and followed "the less severe ones." These observations as well as those of the Joint Study referred to earlier[5] contrast with the present study.

Levin and Sondheimer[8] selected 60 patients from their larger carotid endarterectomy experience. These were patients with a lesion contralateral to the operated side which was measured arteriographically to be greater than 50% stenotic. In this group of 60 patients, there were no strokes and only two patients required an endarterectomy contralateral to the original operation. These were both done for transient ischemic attacks.

This study demonstrates little relationship between the degree of contralateral stenosis and recurrent neurological symptoms after carotid endarterectomy. This is true whether the contralateral artery is totally occluded, partially occluded, or not stenotic at all. These data would suggest that operative intervention is not required in the asymptomatic patient regardless of the degree of contralateral carotid stenosis.

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A New Nonpenetrating Ballistic Injury

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A new, nonpenetrating ballistic injury mechanism involving individuals protected by soft body armor is described. Experimental studies using laboratory animals have demonstrated that despite stopping missile penetration, the heart, liver, spleen, and spinal cord are vulnerable to injury. The rapid jolting force of an impacting bullet is contrasted with the usually encountered mechanisms producing blunt trauma injury. The experimental methodology used to assess a 20% increase in survival probability and an 80% decrease in the need for surgical intervention with a new soft body armor is reviewed. Five cases of ballistic assaults on law enforcement personnel protected by soft body armor are presented. Four emphasize the potentially lifesaving qualities of the armor, while the fifth indicates the need for torso encircling design. Hospitalization should follow all assaults, regardless of the innocuous appearance of the skin lesion and the apparent well being on the assaulted individual. Therapeutic guidelines for patient management are suggested.

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SINCE THE 1960's, an increasing number of police officers have been assaulted with firearms. Attempts against the lives of public officials have also marred this period, including the assassinations of a president, a presidential candidate, and a prominent civil rights leader.

The handgun represents the most commonly used weapon in assults against police personnel. F.B.I. statistics for the ten year period from 1964 through 1973 showed that 74% of police fatalities involved handguns. The "common" handguns and "Saturday night specials" (.38, .380, .32, .25, .22 caliber) represented 81% of the handguns used in the fatal police assaults.[18]

In 1973, a multi-institutional program, the US Army Land Warfare Laboratory (LWL) and the Law Enforcement Assistance Administration (LEAA), was initiated to develop a new lightweight, inconspicuous, soft body armor. Armors then available were generally of the heavy, bulky military type.

After ballistic tests using various materials, a lightweight synthetic fiber, Kevlar-29® (Dupont), was selected for use in body armor fabrication. Seven layers of this high tensile strength material consistently prevented penetration by a .38 caliber missile at 800 ft/sec and a .22 caliber missile at 1000 ft/sec (Fig. 1).[14]

In addition to ballistic studies, biologic and mathematical methodologies assessing the protective qualities of a seven layer Kevlar soft body armor were developed at the US Army's Biophysics Division (Edgewood Arsenal).

Experimental Group
Materials and Methods

Animal experiments were conducted in accordance with the *Guide for Laboratory Animal Facilities and Care*.† These studies were carried out on anesthetised, intubated goats weighing approximately 40 kg. Goats protected with Kevlar armor were assaulted with .38 caliber 158 grain lead bullets at velocities of approximately 800 ft/sec. Shots were targeted over various parts of the body to assess the blunt trauma produced behind armor that defeats a missile, *i.e.*, prevents penetration. Threats to the lungs were targeted over the lateral chest in the sixth or seventh intercostal spaces. Cardiac threats were targeted on the "cardiac window" during end expiration. Intestinal threats were targeted on the midanterior abdominal wall, while hepatic and splenic threats were directed, respectively, to the right and left lower lateral thoracic cage in the eleventh intercostal space. In addition, strikes over the protected spinal column were carried out.

Presented at the 1st National Symposium on Traumatology, May 12, 1978, Baltimore, Maryland.

Sponsored by Law Enforcement Assistance Agency (LEAA) under U.S. Army-LEAA inter-agency agreements No: LEAA-J-IAA-005-4.

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Submitted for publication: March 13, 1978.

† Department of HEW publication (NIH 7323).

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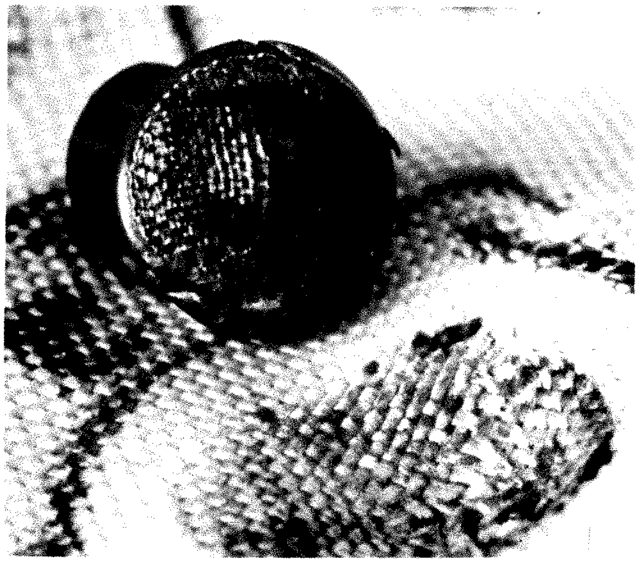

FIG. 1. Deformed .38 caliber bullet following impact at 811 ft/sec on Kevlar material. Note the weave impression of nonpenetrated material imparted to the missile.

In each series of shots, various parameters were monitored depending upon the organ under study. In the cardiac shots, ECG's, cardiac outputs, arterial blood gases, and enzymes were monitored. In the pulmonary shots, arterial blood gases were measured. Neurologic assessments were made following the spinal shots. In all studies, the systemic blood pressure and the parameters peculiar to each study were measured pre- and postassault, one hour after assault, and prior to sacrifice which was carried out at 24 hours. In the spinal shots sacrifice occurred at 48 hours. In all cases, immediate necropsy was performed.

Experimental Group
Results

Typical skin wounds, behind the unpenetrated armor, consisted of an area of superficial laceration about 2–4 cm in diameter surrounded by an ecchymotic and erythematous area. Lacerations occasionally extended into the underlying thoracic and abdominal wall muscles, but penetration into these cavities was not seen.

Necropsy demonstrated the following injuries:

1) Four of eight assaults over dilated bowel resulted in perforations, while in eight assaults over nondilated bowel no perforations occurred. Minor serosal and omental contusions were seen in this latter group.[9]

2) Assaults over the liver produced liver contusions or singular small fractures in 14 of 18 cases. Two associated, nondisplaced rib fractures were also noted. The amount of injured tissue averaged less than 50 cc. No more than 100 cc of blood was found in the abdominal cavity in any case. Although many of these injuries would have required laparotomy in humans, it was estimated that a marked reduction in morbidity and mortality would have been produced by armor protection, since the singular injuries were small and not associated with significant hemorrhage.

3) In 25 thoracic shots, small pulmonary contusions (20 cc or less) were seen in 20 cases. The largest lesion measured 96 cc of excised tissue. In addition, in six cases singular nondisplaced rib fractures were seen. In all cases, no significant changes in arterial oxygenation or systemic blood pressure were encountered.

4) In two of seven initial cardiac tests, a stiff, indwelling left ventricular end-diastolic catheter was felt to be the iatrogenic source of aortic root injuries seen. In 15 subsequent tests (after removal of the catheter), one significant injury was noted—disruption of two aortic valves. This animal demonstrated moderate hypoxemia prior to sacrifice. One animal without evidence of a myocardial contusion demonstrated transient PVC's prior to sacrifice. In all other cases, no conduction defects or arrhythmias were seen.[17]

5) The spleen proved to be an elusive target. Three attempts were made to hit this small organ which has a variable orientation in the goat. In one case, a 2 cm contusion was demonstrated on the inferior edge of the spleen. In the two other cases, no damage was seen in one, and in the other there was poor targeting.[9]

Since the spleen is a friable organ, it is expected that a hit over this organ in the human could result in at least a contusion or subcapsular hematoma. Both of these injuries could eventually lead to laparotomy.

6) Seven of seven shots over the spinal column resulted in isolated spinous or transverse process fractures. In four shots demonstrating spinous process fractures, no neurologic deficits were noted. In three shots producing transverse process fractures, transient hind leg paresis was evident. In two cases, the weakness disappeared in about one hour and, in the third, resolved within 24 hours. In none of the spinal shots was morphologic or histologic evidence of spinal cord injury demonstrated.[9]

Because of the relatively larger size of the spinous processes in goats compared to man, it is estimated that the goat is provided with better protection against blunt trauma injury. Hence, a shot over the human spinal column could possibly result in weakness or even contusion of the spinal column. To more accurately predict the results of a human spinal column impact, another species with similar spinal anatomy should be used in ballistic tests.

The innocuous appearance of typical skin lesions occurring behind the armor did not correlate with the presence or absence of internal injury.

Clinical Correlation

In addition to the above studies, a mathematical methodology was developed relating surface areas of the body protected by the armor with the probability of injury to underlying organs, with and without protection. The probable necessity of surgical treatment was also calculated (Table 1).[9]

Organs considered to be vulnerable in man were those organs which demonstrated injury in the goat ballistic studies. According to the experimental data, these included the heart, liver, spleen, and spinal cord. A kidney impact may produce a small contusion requiring hospital observation with negligible mortality. The lungs and nondilated gastrointestinal tract were not considered vulnerable when protected by the Kevlar armor.

The Law Enforcement Assistance Administration (LEAA) began a field evaluation of the Kevlar armor in December of 1975. In 15 cities, selected on the basis of police assault rates and environmental factors, law enforcement personnel were issued Kevlar soft body armors.

To date, a medical and ballistic assessment team from the Edgewood Arsenal has investigated five assault incidents.

Case Reports

Case 1. A 33-year-old policeman was assaulted with a handgun upon interrupting a burglary in progress. Two .38 caliber, 158 grain lead bullets struck his chest without penetrating his seven layer LEAA garment. The assaults occurred at an estimated range of less than four feet. After impact, the officer was able to pursue his assailant. He experienced no loss of consciousness or dyspnea.

TABLE 1. *Probability of Survival and Necessity of Surgery with and without Armor*

Probability	Per Cent
Survival	
with armor	95–99
without armor	75–93
Surgery	
with armor	7–10
without armor	82–100

Since these calculations were based on pessimistic estimates of pathology, the protective qualities of the Kevlar armor are thought to be better than indicated.

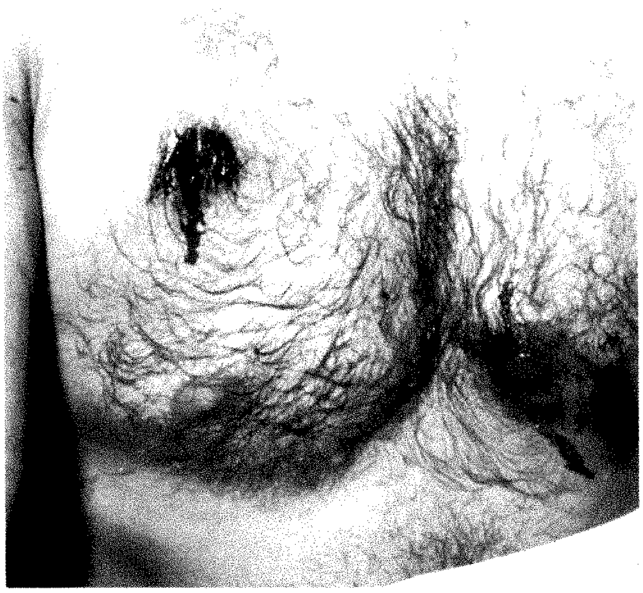

FIG. 2. Skin lesions noted in emergency room immediately after assault on Case I (courtesy of P. E. Besant-Matthews, M.D.).

Behind the armor, two wounds were noted: a 3 × 4 cm lesion located on the right chest slightly lateral to the midclavicular line at the level of the second intercostal space, and a 6 × 4 cm lesion noted over the left sternal border at the level of the fourth intercostal space. Both wounds showed areas of contusion, abrasion, and superficial central laceration, similar to the lesions seen in the animal tests (Fig. 2). Soon after hospital admission, an orthopedic procedure for an associated left hand wound was performed under regional anesthesia. No cardiac irregularities were noted during surgery or in subsequent 24 hour period of cardiac monitoring. An initial arterial blood gas and subsequent serial ECG's, chest x-rays, and isoenzyme determinations revealed no evidence of cardiac or pulmonary injury. The patient was discharged on the third hospital day.

Case 2. A 28-year-old policeman was assaulted with a handgun while investigating a burglary. A 40 grain, .22 caliber missile delivered at a range of about six feet did not penetrate the officer's seven layer Kevlar armor. (Subsequent chronography of the weapon revealed a muzzle velocity of 1136 ft/sec.) After the impact over the left chest, the officer, experiencing only slight wound discomfort, pursued his assailant. Hospitalization for observation of possible intrathoracic injury followed. A 2 × 3 cm wound exhibiting abrasion and central laceration was noted behind the armor one inch lateral to the left nipple (Fig. 3). The patient was placed in a cardiac care unit for 24 hours of monitoring. No cardiac ectopy was seen. Vital signs remained stable. Serial ECG's, chest x-rays, and isoenzyme determinations were within normal limits. The patient was discharged 48 hours after the ballistic assault.

Case 3. A 46-year-old policeman was assaulted while searching for a gunman in a darkened restaurant. The officer's armor, composed of 14 layers of Kevlar and two of ballistic nylon, with front and back panels, lacked lateral torso protection. The officer was struck twice at a range of four to five feet. The first missile consisted of pellets from a .38 caliber "shot shell." A few of these pellets struck the left front panel resulting in no armor penetration or evidence of underlying tissue damage. A second .38 caliber bullet tunneled subcutaneously through the lateral right thorax and exited striking the edge of the back panel. Postassault

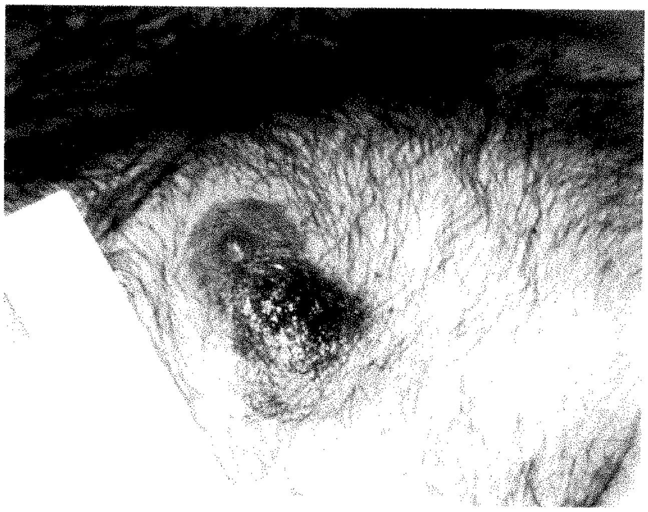

FIG. 3. Skin lesion noted in emergency room immediately after assault in Case II. (courtesy of D. K. Wiecking, M.D.).

dyspnea did not occur, and the patient was unaware of his chest wound until hospitalized. Vital signs on admission were stable and remained as such. The patient also sustained pellet wounds of the left arm, shoulder, and face area. These missiles embedded subcutaneously, causing discomfort but no serious injury. Serial chest x-rays were within normal limits, and the patient was discharged on the second hospital day.

Comment

In addition to the three cases presented in the LEAA field evaluation program, two additional incidents of assault against commercial soft body armors were investigated.

Case 4. A 30-year-old policeman was shot over the lower sternal area while making a traffic investigation. The .38 caliber missile delivered at a close range became embedded in the officer's vest after penetrating two of its eighteen layers of ballistic nylon. A second missile struck the unprotected left shoulder and lodged in the musculature of the right posterior neck. After impact, the officer was able to take protective action. Hospitalization followed the assault. A 4.5 cm circular contusion with superficial laceration was noted over the right xiphoid margin. No radiographic or electrocardiographic evidence of intrathoracic trauma was noted. The patient was discharged on the third hospital day.

Case 5. A 26-year-old policeman was shot with a handgun over the right thoracic cage while wrestling with a criminal suspect. His 15-layer Kevlar armor was not penetrated. After the point blank assault, the officer continued the struggle and arrested the assailant. The missile, a 125 grain, jacketed hollow point .38 caliber bullet, produced a 5 × 5 cm area of contusion and abrasion on the right lateral chest wall over the sixth costal-chondral junction. Upon hospitalization, physical examination and serial radiographs revealed no evidence of intrathoracic injury. Discharge occurred on the second hospital day.

Discussion

In the defeat of a bullet by Kevlar armor, kinetic energy must be dissipated. Energy is expended in deformation of the missile, armor, and underlying body wall, transferred to the body, and lost as heat. On impact, the armor is pushed against the body wall, forcing both inward. Studies were carried out at the Edgewood Arsenal, Biophysics Division, to define the configuration of the deformed Kevlar armor. This deformation, defined as the "backface signature" of the armor, was studied using high speed photography. Motion pictures of backlighted 20% gelatin blocks documented the deformation of the armor into the gelatin when impacted by a missile. Analysis revealed the depth and shape of the deformation, including the time required to reach maximal depth of penetration. These studies demonstrated a symmetric conical deformation of the armor into the gelatin when struck at 0° obliquity.

With seven layers of Kevlar material: in 17 shots using 158 grain, .38 caliber bullets with an average velocity of 251 m/sec (822 ft/sec), having a kinetic energy of 322 joules (237 ft-lbs), a maximal "backface signature" deformation was reached in an average of 1.7 millisec (S.D. ± 0.002).[13]

The deformed cone of armor, smashing into the body wall, over a discrete area in a short interval, describes a unique mechanism capable of producing trauma. This rapid jolting force focused on a small area, much like an "impulse," contrasts greatly with the usually encountered mechanisms producing blunt trauma injury, *i.e.*, those delivered by large objects, over large areas, with relatively prolonged periods of force application.

A host of methodologies has been described to produce experimental blunt trauma to the torso. Some methods have centered on explaining the pathophysiology of blast injury,[2,20] while others have addressed themselves to injuries produced when blunt objects strike the body. Much of this latter work has been directed at characterizing trauma seen in vehicular accidents, such as the steering column injury. These techniques include: striking the exposed heart *in vivo*,[3] striking the perfused liver,[19] strikes to the precordial area,[6,7,11] ramming the abdomen of a stationary animal with a blunt object,[19] and propelling an animal into a blunt object.[8]

Thus, previous methods used to produce blunt trauma generally employed large objects impacting large surfaces. In addition, the application of force was generally over a long period of time relative to the 2 msec "impulse" in the ballistic studies.

Much of the blunt trauma experience in the clinical literature is not comparable to that seen behind a pliable body armor. Series presenting blunt trauma injuries of the heart,[5,10] aorta,[15] lungs,[1] liver,[12,16] and intestines[4] are heavily weighted by vehicular trauma. However, clinical and research experience in blunt trauma is not to be dismissed when considering blunt injury relative to soft body armor. This vast experience has documented the insidious nature of blunt trauma injury.

Although the assessment of the protective qualities of a soft body armor prototype continues, the results of the cases presented in this report are most encouraging.

In cases 1, 2, and 4, a projectile directed at or near the heart and great vessels at close range was easily defeated by the armor. Had penetration occurred, a serious chest wound necessitating emergency surgery would have resulted. A fatal outcome could have been postulated in each case. However, surgery was avoided (except for an associated hand wound), and hospitalization was short. In case 5, the armor prevented penetration by a missile directed at an area occupied by both the lung and liver.

The injuries sustained by the policeman in case 3, although fortunately not serious, convinces us that a torso encircling armor with lateral protection is the best protective design.

A new lightweight soft body armor appears to lower the morbidity and mortality from certain ballistic threats. We feel, however, that a new injury mechanism and clinical presentation have been defined. Based on studies using laboratory animals, the severity of underlying injury may not correlate with the seemingly innocent skin lesions. Therefore, in the case of impact on a soft body armor, it is recommended that 1) all victims of assault should be hospitalized for observation in spite of an apparent state of good health and a minimal skin lesion. 2) Strikes to the chest should be monitored with serial chest x-rays. 3) Strikes to the precordial region require cardiac monitoring and serial ECG's and enzyme determinations. 4) Strikes to the abdomen require frequent examination for signs of peritoneal irritation. Impacts over the liver should be viewed with great suspicion of underlying hepatic injury.

Acknowledgments

The authors gratefully acknowledge the assistance of C. Edward Hawkins and Russell Prather.

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Alterations in Plasma Norepinephrine Concentration During Surgical Resection of Pheochromocytoma

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Using a sensitive and specific radioenzymatic assay, the plasma norepinephrine (NE) concentration was measured in seven patients with pheochromocytoma, one patient with bilateral adrenal medullary hyperplasia, one patient with a retroperitoneal paraganglioma, and two patients undergoing bilateral adrenalectomies for palliation of metastatic breast carcinoma. Surgical manipulation of the pheochromocytomas resulted in striking increases in plasma NE concentration with concomitant increases in blood pressure. There were either small changes or no changes in the patients' plasma NE and blood pressure during resection of the normal adrenal glands, the adrenal glands with medullary hyperplasia, or the retroperitoneal paraganglioma. Plasma dopamine-β-hydroxylase (DBH) was measured in one patient with pheochromocytomas and the patient with medullary hyperplasia. There was no change in plasma DBH in either patient, supporting the concept that exocytosis is not the primary mechanism for catecholamine secretion from pheochromocytomas. It was also noted that enflurane is an excellent general anesthetic for the resection of pheochromocytomas, and that sodium nitroprusside (rather than phentolamine) may be the agent of choice for the management of the hypertensive episodes that occur during surgical manipulation of pheochromocytomas.

THE DEVELOPMENT of specific and sensitive methods for the measurements of catecholamines and their metabolites in urine and plasma has facilitated the evaluation of patients with suspected pheochromocytomas (pheos). However, pheos have remained a diagnostic challenge for the internist and surgeon, as these tumors must be suspected on clinical grounds in order that the appropriate diagnostic tests can be obtained. Once diagnosed, the definitive therapy is surgical excision of the tumor. Although our knowledge of the surgical management of pheos has expanded considerably since Dr. Charles Mayo performed the first resection of such a tumor in 1926 these neoplasms are still a therapeutic challenge fo surgeons and anesthesiologists.[17] During inductio of anesthesia or surgical manipulation of their tumors patients with pheos may have wide swings in bloo pressure (BP) and heart rate (HR). These dramati changes in BP and HR are thought to be due t secretion of massive quantities of catecholamines such as norepinephrine (NE) and epinephrine (E) that are stored in the tumor. The surgical mortalit rate of patients with unsuspected pheos who underwent an unrelated operation was 50%.[2] Prior to 1951 the surgical mortality rate of patients with a correc preoperative diagnosis who were undergoing resectio of their pheos was 24%.[2]

The high mortality rate associated with resection o pheos was due in large part to the general unavailability of effective adrenolytic agents. However even after alpha-adrenergic antagonists, such a phenoxybenzamine, came into use in 1952, a hig operative mortality rate of 13% was noted in on collected series of 282 cases.[12] Recently, with th recognition of the importance of intraoperative an postoperative fluid volume replacement, the mortalit rate has been further reduced to 2.9%.[24]

In this report, we describe our experiences wit the surgical management of seven patients with pheos one patient with bilateral adrenomedullary hyperplasia, and one patient with an NE secreting retroperitoneal paraganglioma. We have monitored th plasma level of NE in the intraoperative period using a sensitive and highly specific radioenzymatic assay Although surgical manipulation of the tumor durin resection was associated with dramatic increase

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Supported by the Veterans Administration (2650-1), a grant from the Clinical Research Center Branch Divisions of Research Facilities and Resources, U.S. Public Health Service (M01-RR-30) and NIH Contract CB-63994-39.

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Submitted for publication: April 6, 1978.

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in plasma NE concentration, the preoperative and intraoperative management that was used resulted in a smooth course in all but one of the patients.

Materials and Methods

Patients

The nine patients with catecholamine-secreting tumors (seven men, two women) ranged in age from 16 to 55 years (mean age 36 years). Five of the patients had multiple endocrine neoplasia Type 2 (MEN II)[28]: that is, bilateral pheos associated with medullary carcinoma of the thyroid (MCT). Patient 4 had undergone partial thyroidectomy four years before. The other patients had not had thyroid surgery at the time their pheos were resected. Their basal thyrocalcitonin levels (plasma TCT concentrations) ranged from 0 to 2 ng/ml (mean 0.5 ng/ml). Their plasma TCT ranged from 3 to 380 ng/ml (mean 91 ng/ml),[31] three minutes after stimulation with one minute infusion of calcium gluconate (2 mg Ca^{++}/kg) followed by a five second injection of pentagastrin (0.5 μg/kg). As plasma TCT is not detectable in normal subjects under both of these test conditions, the elevated plasma TCT concentration indicates the presence of MCT tissue.[31] None of the patients had evidence of any distant metastasis from the MCT.

Patient 7 had sporadic bilateral pheos. His thyroid was normal to examination; his plasma TCT was undetectable in the basal state and after the administration of calcium gluconate and pentagastrin. Patients 1 and 6 had sporadic unilateral pheos. Patient 9 was a 16-year-old girl with a right-sided retroperitoneal mass of unknown etiology. A catecholamine-secreting tumor was not suspected until shortly prior to surgery; thus, preoperative levels of urinary excretion of catecholamines and their metabolites were not available for this patient.

Five of the patients underwent preoperative evaluation on the Duke Clinical Research Unit; three patients were evaluated on the general medical wards at Duke; and one patient was evaluated on the general medical wards at the Durham VA Hospital. After entering the hospital, 24-hour urine samples were collected under constant refrigeration. Blood samples, collected in ethylenediamine tetra-acetic acid anticoagulant (EDTA), were drawn through an indwelling needle after the patients had been supine for 30 minutes, with the exception of patients 6 and 9. Blood samples from these two patients were obtained after they had been supine for at least 30 minutes on the morning of surgery. The plasma was separated by centrifugation and frozen (−28°) until it was analyzed.

With the exception of patient 9, all patients received oral phenoxybenzamine (DBZ) prior to surgery, in doses ranging from 20–60 mg/day. DBZ was administered on the morning of surgery. Only two of the eight patients received propranolol in the preoperative period: patient 1 received 40–120 mg/day for seven days prior to surgery; patient 2 received 60 mg/day for the nine months preceding surgery. All of the patients, except patient 9, received intramuscular injections of 200 mg of cortisone acetate for two days preceding surgery, as well as on the morning of surgery.

With the exception of patients 7 and 9, all of the patients were operated on by the same surgeon (S.A.W.). With the exception of patient 7, all of the patients had a similar anesthetic regimen administered by the same anesthesiologists (L.F. and J.N.M.).

The preoperative medication was 10 mg intramuscular diazepam (Valium®), and 10 mg morphine sulfate. Atropine was not used in seven of the patients. Enflurane (Ethrane®) and nitrous oxide:oxygen mixture (3:2) were used for general anesthesia in all patients except patient 7. An arterial catheter was inserted in the radial artery prior to anesthesia induction and attached to a Grass recorder for continuous recording of BP and HR, and to obtain blood samples for arterial blood gas and plasma NE (EDTA) estimations; a central venous catheter was inserted for measurements of central venous pressure; catheters were inserted in peripheral veins for fluid and blood replacement and drug administration. In two cases, arterial blood samples were drawn for determination of DBH activity (patients 3 and 8). These arterial blood samples were obtained at intervals throughout the surgical procedure; additional samples were obtained at times when there was a significant alteration in BP or HR. In addition, blood samples were usually obtained for three days after the surgical procedure.

Patient 7 was under the care of a different anesthesiologist and surgical team. He was the only patient in this series with a significant anemia (hemoglobin 8.3 g/dl and packed red cell volume 27%). This was thought to be due to iron deficiency with no site of blood loss uncovered. He received 4 U packed red blood cells two days prior to surgery. His preoperative medications were 10 mg diazepam and 0.6 mg IM atropine sulfate. The anesthetic agents were sodium thiopental (Pentothal®), fentanyl with droperidol (Innovar®) and nitrous oxide:oxygen (2:1). This patient's BP measurements were made with a sphygmomanometer rather than an intra-arterial line.

To determine if the anesthetic agents or adrenal gland manipulation alters plasma NE concentration in patients without pheochromocytomas, peripheral venous blood samples were obtained from two women (age 60) during bilateral adrenalectomies for metastatic breast carcinoma. The same surgeon operated on these patients and the same anesthesiologists administered anesthesia by similar techniques as they did for all but one of the patients in the study. However, the bilateral adrenalectomies were performed through two flank incisions, rather than through the transabdominal incisions used for the resection of the pheos.

The normal range for plasma NE was established by obtaining blood samples from 14 healthy subjects (seven men and seven women), ranging in age from 17 to 48 years (mean age 31 years). After lying supine for 30 minutes, the venous blood sample was drawn from an indwelling catheter. The normal range for plasma DBH was established by obtaining blood samples from a second group of 13 healthy subjects (eight men and five women), ranging in age from 23 to 61 years (mean age 37 years). These subjects were ambulatory just prior to drawing the blood samples with a venipuncture. There is no difference in plasma NE and plasma DBH in brachial arterial and brachial venous blood. The normal range of excretion of catecholamines and their metabolites was previously established by our laboratories (Table 1).

Analytical Methods

Twenty-four-hour urine samples were analyzed for epinephrine (E),[29] NE,[29] metanephrines,[22] vanillylmandelic acid (VMA)[23] and homovanillic acid (HVA).[25] Plasma samples were analyzed for DBH activity,[19] TCT,[31] and NE.[11] Pheos were analyzed for DBH activity,[16] E,[1] and NE.[11]

The radioenzymatic method for measuring NE in plasmas and tissues utilizes the enzyme phenylethanolamine-N-methyltransferase (PNMT) that we partially purify from fresh bovine adrenal glands.[11] The PNMT transfers a ^{3}H-labeled methyl group from ^{3}H-S-adenosyl-methionine (New England Nuclear, Boston, Massachusetts) to NE in plasma or tissues. Because of the differences in the nonradioactive S-adenosyl-methionine content of different tissues, each sample is quantitated by its own internal standard. The assay is highly sensitive and specific; there is less than 2% cross reactivity with E, dopamine, serotonin or L,3,4-dihydroxyphenylalanine. None of the medications that the patients received are measured by or interfere with this assay.

The total DBH activity and total NE and E contents of each pheo were determined by multiplying the DBH activity or NE content per gram of tumor by the total weight of the tumor in grams. The DBH activity and NE content of the two pheos were added together to give the total DBH activity and total NE content.

Statistical Analysis

Correlation analysis was done with the Pearson product correlation coefficient®.[33]

Results

Table 1 summarizes the clinical and laboratory characteristics of the patients. Six of the patients had histories of hypertension or had hypertension during their hospitalization periods; three patients did not have any evidence of hypertension. The studies of excretion of urinary catecholamines or their metabolites revealed the following: Three of eight patients had elevated urinary E excretion; six of eight patients evaluated had elevated NE excretion; five of six patients had elevated urinary total metanephrine excretion; all patients evaluated had elevated VMA excre-

TABLE 1. *Clinical and Laboratory Characteristics of Patients with Pheochromocytomas*

			Urinary Excretion					
			E	NE	Metanephrines	VMA	HVA	
Patient	Hypertension	Medullary Carcinoma of the Thyroid	← (μg/24 h) →		←———— (mg/24 h) ————→			Plasma NE (pg/ml)
1	Yes	No	0	2354	*	37.8	*	4905
2	Yes	Yes	315	1325	10.5	59.2	4.8	4066
3	No	Yes	136	159	7.5	19.0	4.8	715
4	Yes	Yes	22	43	2.9	8.8	3.3	260
5	Yes	Yes	50	39	6.9	13.0	4.6	709
6	Yes	No	5	304	*	21.0	*	846†
7	No	No	0	250	0.8	8.5	21.5	241
8	No	Yes	17	64	1.8	12.0	4.0	335
9	Yes	No	*	*	*	*	*	3067†
Patient Mean			68	567	5.1	22.4	7.2	1683
Normal Range			5–25	20–50	<1.6	<6.0	2.3–9.5	30–417

* Not measured. †Morning prior to surgery.

TABLE 2. *Relationship Between Size and Catecholamine Content of Pheochromocytomas and the Maximum Plasma NE Concentration During Resection of the Pheochromocytoma*

	Right Pheochromocytoma				Left Pheochromocytoma			
Patient	Weight (grams)	E Content (mg)	NE Content (mg)	Max. Plasma NE During Resection (pg/ml)	Weight (grams)	E Content (mg)	NE Content (mg)	Max. Plasma NE During Resection (pg/ml)
1	†	†	†	†	135§	*	*	92,888
2	113	0	701	127,323	74	175	182	13,258
3	10	2	70	3,122	32	5	480	108,504
4	15	7	117	32,007	1.8	5	2	2,058
5	30	12	262	31,157	10	23	12	4,923
6	29	0	61	10,516	†	†	†	†
7	14.5	0	0.16	1,681	160	0	0.64	5,530
8	2§	*	7	654	2§	*	6	621
9	125‡	*	*	*	†	†	†	3,369
Patient Mean	30.5	3.5	174	29,494	59	42	114	28,894

* Not measured. †Not present. ‡Estimated weight, based on actual measured dimensions (7.2 × 5.0 × 3.8 cm.) §Estimated weights, based on actual measured dimensions (7.5 × 6.5 × 3.0 cm).

tion; one of six patients had elevated urinary HVA excretion; and six of eight patients had elevated basal plasma NE concentration.

Table 2 summarizes the findings at surgery. Five of the patients had bilateral pheos; two patients had unilateral pheos; one patient had bilateral adrenal medullary hyperplasia; and one patient had a retroperitoneal paraganglioma. The pheos ranged in weight from 1.8 to 135 g; the total E content of the pheos ranged from 0 to 17 mg; and the total NE content ranged from 0.2 to 701 mg. The total NE content was greater than the total E content in ten of the 12 tumors evaluated. The only tumors in which the total E content was greater than the total NE content were the left tumors of patients 4 and 5. In both of these patients, the left pheo was smaller than the right pheo.

The relationship between the surgical events, plasma NE concentration, BP, HR and the pharmacological treatment is summarized in the figures depicting each surgical procedure. The total NE content of each pheo, except for that of patient 1, is included on the figure the first time the pheo is manipulated. This gives some notion of the relationship between the quantity of NE in the tumor and the alterations in plasma NE during its manipulation and resection. The order in which the patients are presented is in general determined by the peak plasma NE concentration noted during surgery. It should be noted that the scale of NE measurements on the figures is altered to display the data in the most informative manner.

Case Reports

Patient 1. (Fig. 1) This 36-year-old man who had had hypertension since age 15, had markedly elevated plasma NE concentration and urinary excretion of NE and VMA in the preoperative period. For the eight days preceding surgery, he received only a modest dose of DBZ (40 mg/day). In addition, he received propranolol for the last seven days. During the preoperative period, he developed orthostatic hypotension. Figure 1 shows that manipulation of his tumor induced striking elevations in his plasma NE concentration, and was associated with paroxysms of severe hypertension, alternating with periods of marked hypotension. There were periods of sinus tachycardia, and at 90 minutes into the surgical procedure, he developed a transient nodal tachycardia. During his stormy operative course, he received phentolamine, ephedrine, phenylephrine, propranolol, and a brief infusion of sodium nitroprusside during a bout of severe hypertension. Unfortunately, we were unable to determine the total catecholamine content of his large pheo.

Patient 2. (Fig. 2) This 27-year-old man also had hypertension with markedly elevated plasma NE levels and urinary excretion of NE and VMA in the preoperative period. He received propranolol (60 mg/day) and DBZ (60 mg/day) for nine months prior to surgery. Initial manipulation of his large left pheo resulted in a 38-fold rise in his plasma NE concentration (3,310–127,323 pg/ml). The resulting hypertension was treated immediately with a nitroprusside infusion rather than phentolamine, and the BP returned to normal. The nitroprusside infusion was required for the next 25 minutes. Dissection of the tumor resulted in another dramatic increase in plasma NE concentration to 100,194 pg/ml. However, the nitroprusside prevented the development of hypertension. Manipulation of the smaller right pheo (NE content 186 mg) resulted in a trivial increase in plasma NE. However, this pheo also contained substantial amounts of E (E content 175 mg). The increase in BP that occurred at that time was again rapidly corrected with a brief nitroprusside infusion. In contrast to patient 1, patient 2 had a smooth operative course.

Patient 3. (Fig. 3) Despite moderately elevated VMA and metanephrine excretion in the preoperative period, this 18-year-old man did not have hypertension or a history of hypertension. He was, in fact, asymptomatic; the presence of pheos was uncovered during his evaluation as a member of a family with MEN II. During manipulation of his large left pheo (NE content 480 mg), there was a 135-fold increase in his plasma NE concentration (804 pg/ml to 108,504 pg/ml). However, he had only modest increases in BP that were easily controlled with short infusions of nitroprusside.

During the surgery, we also obtained plasma samples for measurement of DBH. DBH, an enzyme that catalyzes the conversion of

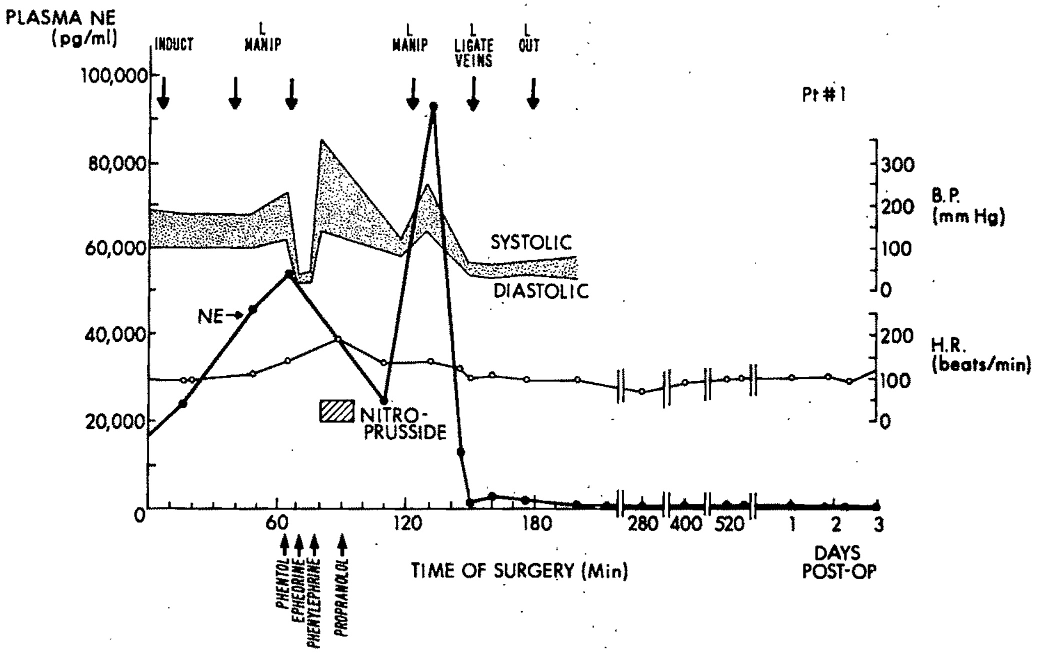

FIG. 1. Relationship between surgical events, plasma NE concentration, BP, and HR during resection of a left pheo in patient 1.

dopamine (DA) to NE, is released from sympathetic tissue and the adrenal medulla during the secretory process.[8,28,30] The lower portion of Figure 3 shows that despite the massive increase in plasma NE during manipulation of the left pheo, the plasma DBH activity remained within the normal range established for our laboratory (4.4–35.0 μmol/min/l) at all times. To rule out the presence of an inhibitor of DBH in the patient's plasma, we performed mixing studies in which we combined the patient's plasma with the plasma of a patient with elevated DBH activity (52.7 μmol/min/g). We observed the predicted additive DBH activity in all mixed samples. Thus, the plasma DBH activity was truly normal throughout surgery.

Analyses of the resected pheos revealed that the DBH activity of the left pheo was 4.6 μmol/min/g and the DBH activity of the right pheo was 9.5 μmol/min/g. Thus, the total DBH activity in the two pheos was 242 μmol/min. The DBH activity of the adrenal medulla tissue obtained from the five normal adrenals resected for palliation of metastatic breast cancer was 1.12 μmol/min/g (range 0.78–1.61 μmol/min/g). Hence, the estimated total DBH activity in the two adrenal glands of a person without a pheo would be 2.24 μmol/min. It is impressive that, although patient 3 had a 108-fold increase above normal in adrenal medullary type of DBH, there was no increase in plasma DBH during manipulation of his pheo.

Patient 4. (Fig. 4) This 55-year-old woman had a 25-fold increase in plasma NE concentration when her right pheo was manipulated (NE content 117 mg). The increase in BP was easily controlled with nitroprusside infusion. There was no alteration in plasma NE or BP when her smaller left pheo was manipulated (NE content 2.3 mg).

Patient 5. (Fig. 5) This 39-year-old man had a 39-fold increase in plasma NE when his right pheo was manipulated (NE content

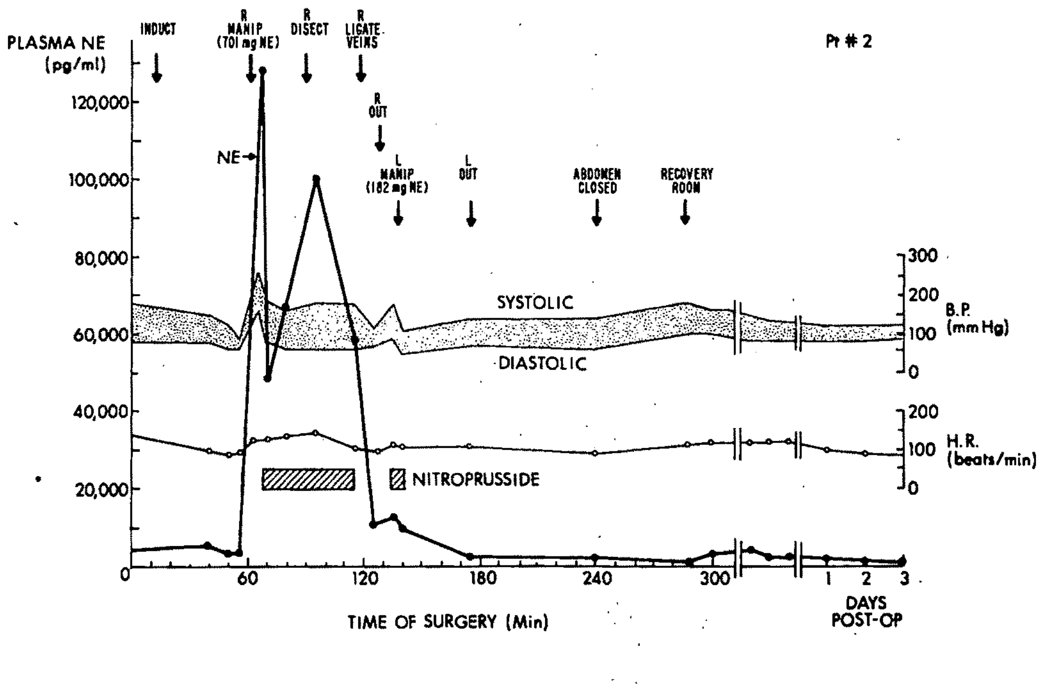

FIG. 2. Relationship between surgical events, pheo NE content, plasma NE concentration, BP and HR during resection of bilateral pheos in patient 2. The numbers in parentheses, at the top of the figure, represent the NE content of each pheo.

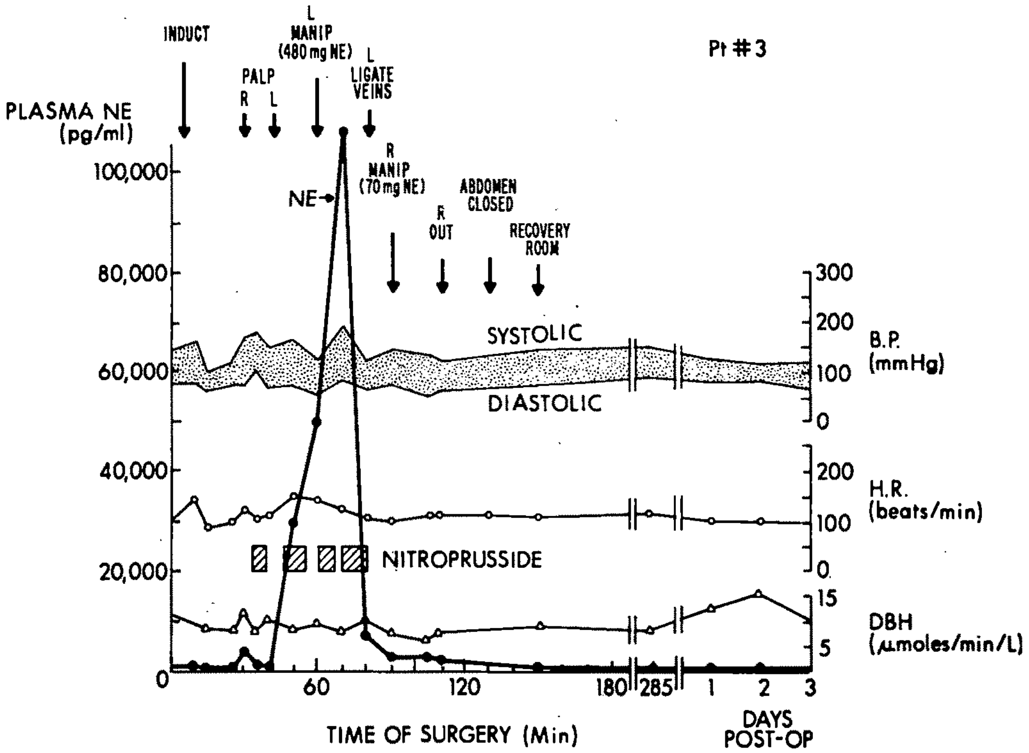

FIG. 3. Relationship between surgical events, pheo NE content, plasma NE concentration, plasma DBH activity, BP and HR during resection of bilateral pheos in patient 3. The numbers in parentheses, at the top of the figure, represent the NE content of each pheo.

262 mg). Nitroprusside controlled the accompanying increase in BP. There was a six-fold increase in plasma NE when his smaller left pheo was manipulated. The accompanying increase in BP was easily controlled by a second brief nitroprusside infusion.

Patient 6. (Fig. 6) This 53-year-old man had a moderate sized sporadic pheo of the right adrenal gland (NE content 61 mg). Manipulation of the tumor resulted in a 54-fold increase in plasma NE concentration (196–10,516 pg/ml). The accompanying increase in BP and HR were easily controlled with nitroprusside drip. The patient's left adrenal gland was found to be normal at surgery. However, three months after surgery, his urinary VMA excretion was still elevated, raising the possibility that he has another pheo in ectopic adrenal tissue or in an extraadrenal site. It is of interest that, despite the possible presence of a second pheo, his plasma NE promptly fell to normal when the right pheo was removed.

Patient 7. (Fig. 7) This 26-year-old nonhypertensive patient represented a most unusual case of pheo. Bilateral suprarenal masses were discovered during a diagnostic evaluation for weight loss and abdominal pain. Prior to surgery, he was noted to have an elevated 24-hour excretion of VMA (8.5 mg) and NE (250 μg). Analysis for urinary HVA was not performed until after surgery. The markedly elevated 24-hour HVA excretion of 21.5 mg indicated that DA was the predominant catecholamine secreted by his pheo. The patient received 60 mg of DBZ for 17 days preceding his surgery. During surgery, he was found to have a large left pheo (160 g) arising from his left adrenal gland and a smaller right extra-adrenal pheo behind the vena cava. The right adrenal gland itself was normal. During the time his large left pheo was manipulated (NE content 0.64 mg), there was a 19-fold increase in plasma NE (285–5,530 pg/ml). This was accompanied by a fall rather than a rise in BP. This fall in BP may have been due to the brisk bleeding from the site of tumor dissection, as well as possible secretion of the potent vasodilator DA during tumor dissection. The rise in plasma NE may be due to reflex stimulation of the sympathetic nervous system by hypotension rather than by secretion from the pheo. There was no alteration in plasma NE or BP during manipulation of the smaller right pheo (NE content 0.16 mg). During the difficult resection of the large left pheo, the spleen and left renal artery were damaged, necessitating a splenectomy and splenorenal artery shunt. Although there was no evidence of distant metastasis, a portion of tumor was extending above the diaphragm. A small opening was made in the diaphragm, and the mass was scooped downward. The tumor was adherent to the vertebral bodies; during dissection, there was considerable bleeding from this particular area. The patient received 23 U of blood during the six and one-half hour surgical procedure. Because of continuing bleeding from his left chest tube in the immediate postoperative period, the patient was returned to the operating room where he underwent a left thoracoabdominal reexploration for bleeding. Residual tumor tissue in the mediastinum, which was bleeding, was removed. During the second operative procedure and the next two postoperative days, the patient received an additional

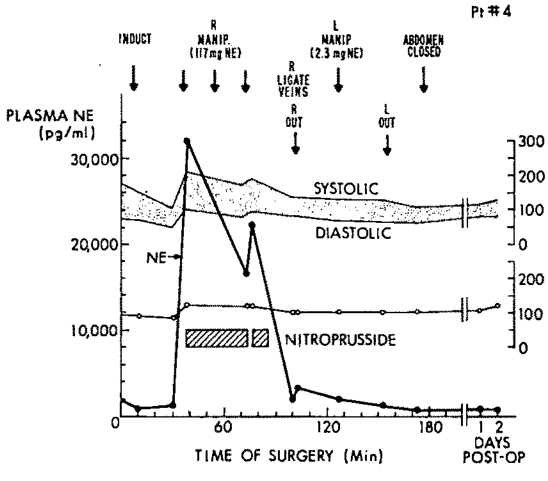

FIG. 4. Relationship between surgical events, pheo NE content, plasma NE concentration, BP and HR during resection of bilateral pheos in patient 4. The numbers in parentheses, at the top of the figure, represent the NE content of each pheo.

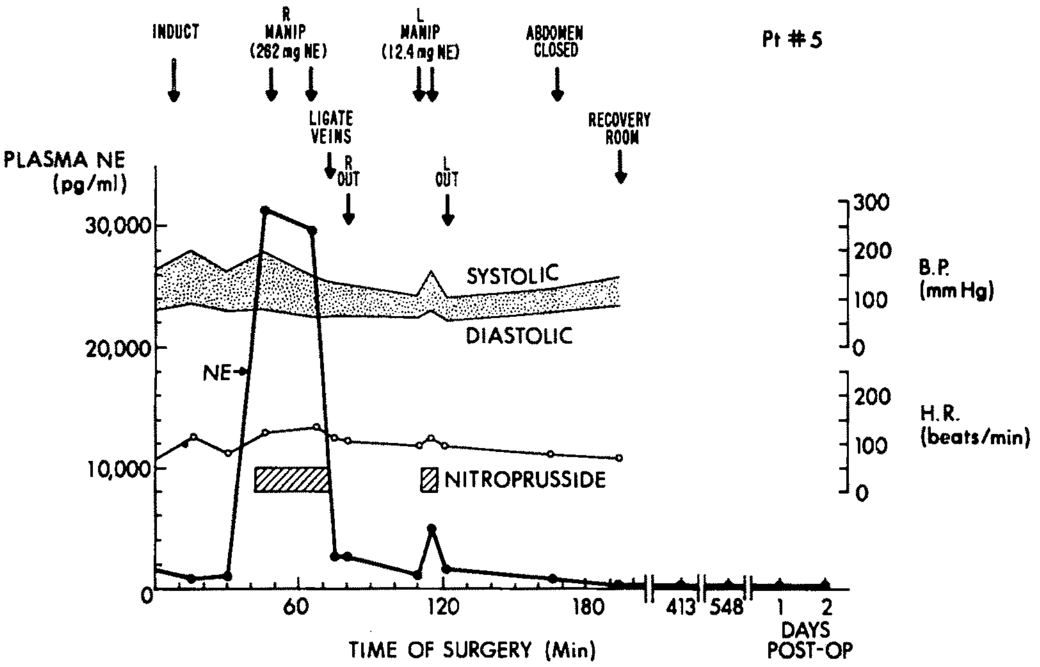

FIG. 5. Relationship between surgical events, pheo NE content, plasma NE concentration, BP and HR during resection of bilateral pheos in patient 5. The numbers in parentheses, at the top of the figure, represent the NE content of each pheo.

22 U of blood. Examination of the tumors by both light and electron microscopy revealed typical pheos. Postoperatively, the patient's 24 hour excretion of HVA (1.8 mg), VMA (2.5 mg), and NE (25 μg) were normal. His abdominal pain is gone and he has started to regain weight.

Patient 8. (Fig. 8) This 55-year-old man had a small MCT. He is a member of a family with MEN II and a high incidence of pheo. Because of his elevated 24 hour urinary VMA excretion (12.0 mg), he was operated on for pheo. At surgery, he was found to have diffuse and nodular hyperplasia of the adrenal medullae.[3] During manipulation of his adrenal glands, there was a two-fold rise in his plasma NE (377–760 pg/ml). This was accompanied by a modest rise in BP that was easily controlled with nitroprusside. His plasma DBH was normal preoperatively, and it did not change significantly during the course of surgery. DBH activity was present in one of the small nodules in his left adrenal (0.35 μmol/g/min). No other masses of chromaffin tissue were found at surgery, and the patient underwent bilateral adrenalectomies and a cholecystectomy for gallbladder calculi that were found.

Patient 9. (Fig. 9) This 16-year-old girl underwent surgery for a right retroperitoneal mass of unknown etiology. A large retroperitoneal paraganglioma was found during abdominal exploration and was successfully resected. The patient had a markedly elevated plasma NE concentration (3,067 pg/ml). It is of interest that the

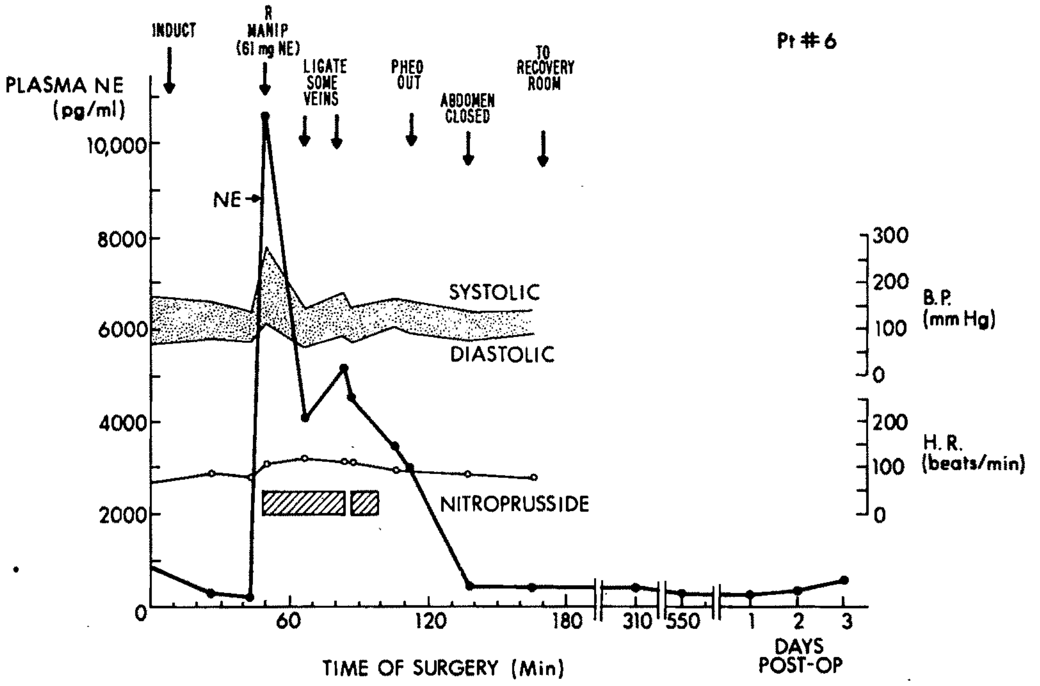

FIG. 6. Relationship between surgical events, pheo NE content, plasma NE concentration, BP and HR during resection of a right pheo in patient 6. The number in parentheses, at the top of the figure, represents the NE content of the pheo.

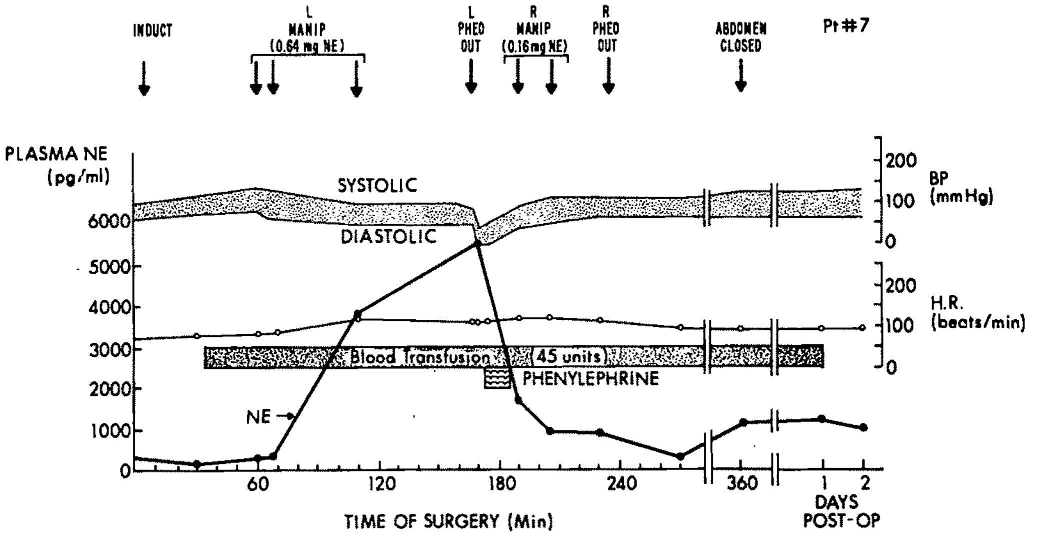

FIG. 7. Relationship between surgical events, pheo NE content, plasma NE concentration, BP and HR during resection of bilateral pheos in patient 7. The numbers in parentheses, at the top of the figure, represent the NE content of each pheo.

plasma NE concentration did not show a significant increase during tumor manipulation (3,369 pg/ml). There was a prompt fall in plasma NE when the final veins draining the tumor were ligated and the tumor was removed.

Patients 10 and 11. (Fig. 10) There were either no changes (patient 10) or small changes (patient 11) during manipulation and resection of the adrenal glands of the patients with metastatic breast cancer. There were only small changes in the blood pressure and pulse of these patients during surgery. There was an increase in plasma NE concentration in the postoperative period in patient; however, this may have been due to postoperative pain.

Induction of anesthesia has been reported to trigger the discharge of catecholamines from normal adrenal glands, as well as from pheos. It is of interest that with the anesthetic regimens used in the present study, induction of anesthesia did not trigger the release of NE in either of the two patients with breast cancer, the eight patients with pheos, or the one patient with a paraganglioma. In the six patients with proven pheos who received enflurane as the primary anesthetic agent, induction of anesthesia was associated with an increased plasma NE concentration in patients 1 and 2 and decreased plasma NE concentrations in patients 3, 4, 5, and 6. The mean change in plasma NE concentration was a decrease of 23% (range of changes —44% increase to a 64% decrease).

To determine if there was any relationship between various features of the pheo and the peak plasma NE encountered during surgery, correlation analysis was carried out. There was a significant correlation between the NE content of the pheo and the peak plasma NE concentration achieved during resection of the pheo ($r = 0.96$, $p < 0.01$). There was no significant correlation between the weight of the pheo and the plasma NE concentration attained during its resection ($r = 0.47$), or between total NE content of the pheo(s) and the preoperative basal plasma NE concentration ($r = 0.20$). We did find a significant correlation between the 24 hour urinary excretion of VMA and the peak plasma NE concentration achieved during surgical resection of the pheo(s) ($r = 0.78$, $p < 0.05$), and there was a significant correlation between the basal plasma NE

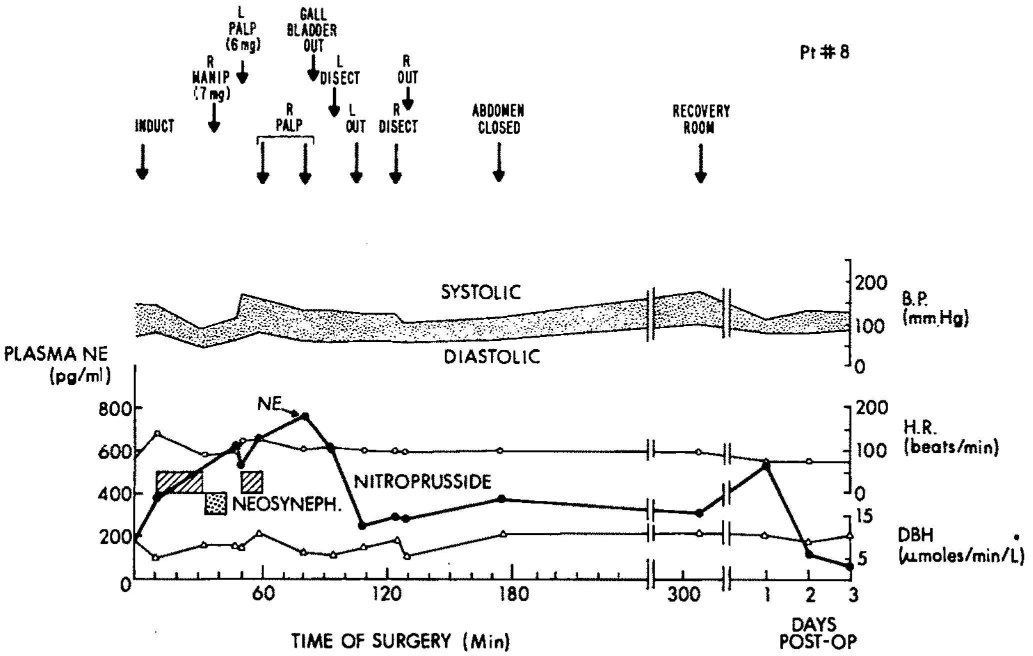

FIG. 8. Relationship between surgical events, estimated adrenal NE content, plasma NE concentration, plasma DBH activity, BP and HR in patient 8 who had bilateral diffuse and nodular adrenal medullary hyperplasia. The numbers in parentheses, at the top of the figure, represent the estimated NE content of each adrenal gland.

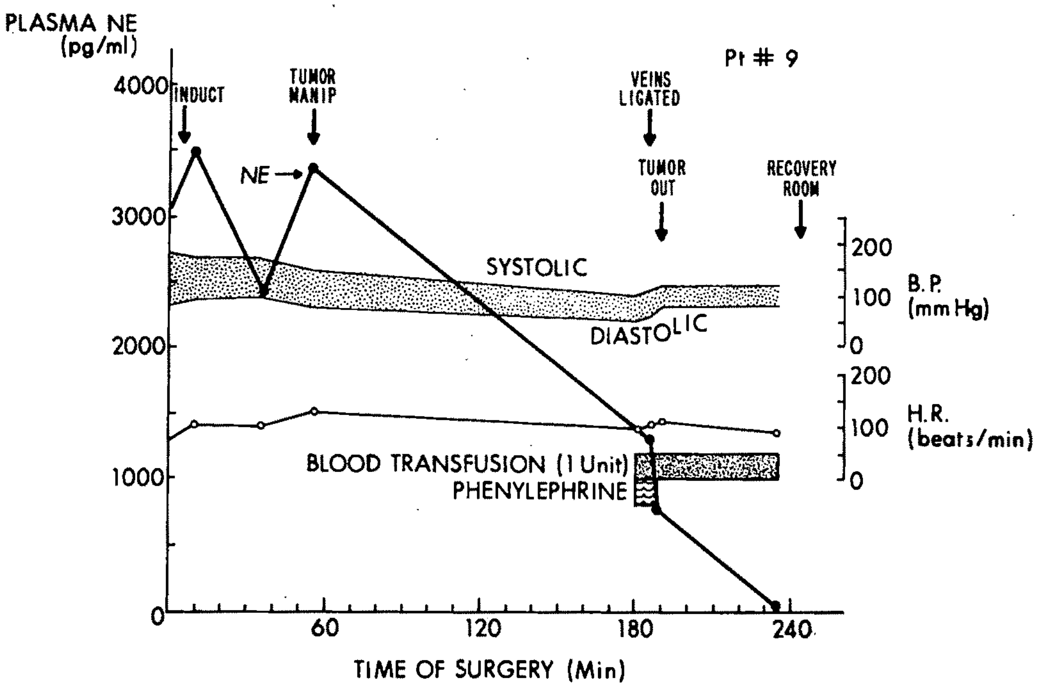

FIG. 9. Relationship between surgical events, plasma NE content, BP and HR in patient 9 who was undergoing resection of a right retroperitoneal paraganglioma.

levels and peak plasma NE achieved during resection of the pheo(s) ($r = 0.80$, $p < 0.01$).

Discussion

The present report demonstrates that there are striking increases in plasma NE during surgical manipulation of pheos. These measurements, made with a specific radioenzymatic assay, confirm and extend the observations that have been made by other investigators with fluorometric methods of catecholamine analysis.[13,15] The radioenzymatic method has greater sensitivity than the fluorometric method. We were able to perform the NE analysis on 2 ml or less of plasma. We obtained more frequent blood samples than some of the previous studies. The multiple blood samples show that the magnitude of the increase in plasma NE is proportional to the NE content and that the increase in BP that occurs during manipulation of the pheo(s) is also closely related to the magnitude of elevation in plasma NE.

DBH, the enzyme that converts DA to NE, is found in the synaptic vesicles of sympathetic neurons[8] and the chromaffin vesicles of the adrenal medulla.[28] During stimulation of sympathetic nerves, there is a proportional release of NE and DBH, suggesting that DBH activity in plasma may provide a quantitative index of catecholamine release that occurs in the usual manner of exocytosis.[30] Despite elevations in plasma NE during manipulation of their pheos (patient 3) or of the adrenal glands in adrenal medullary hyperplasia (patient 8), our patients did not show an increase in plasma DBH activity. This was particularly impressive in patient 3, who had a 135-fold increase in plasma NE during manipulation of his pheo. This observation supports the contention of Winkler and Smith that the process of exocytosis is not involved in the secretion of catecholamines from pheos.[32]

Patient 9 was the only subject in this series with an NE-secreting paraganglioma rather than a pheo. Although her plasma NE concentration was elevated, it did not increase further with manipulation of her tumor. However, she was one of the two patients who were operated on by a different surgeon. Further observations on patients with paragangliomas will be required to decide if different responses to manipulation represent a fundamental difference between pheo and paraganglioma or a difference in surgical technique.

With the exception of patients 1 and 7, all of our patients had smooth operative courses. Patient 1 had a large pheo and was treated with modest, orthostatic doses of DBZ. His intraoperative elevations in BP were mainly treated with injections of phentolamine. Patient 7 had a large tumor that was predominantly secreting DA. If we had known prior to surgery that his pheos were secreting DA, rather than NE or E, we perhaps would not have treated him with DBZ in preparation for surgery. The remaining patients with pheos underwent similar preparation for surgery, as well as similar anesthetic regimens.

The patients received the alpha adrenergic antagonist DBZ for seven to 14 days prior to surgery. This is administered to all patients who have a pheo that, on clinical (hypertension) or laboratory grounds, seems to be secreting NE or E. We concur with the recom-

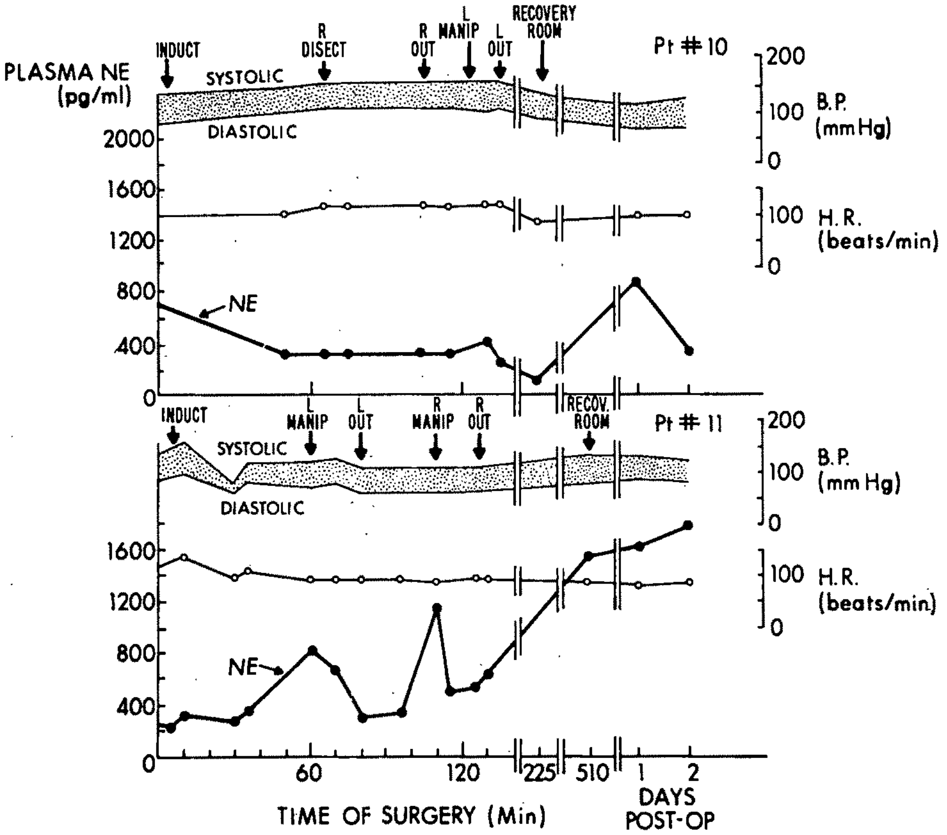

FIG. 10. Relationship between surgical events, plasma NE concentration, BP and HR in patients 10 and 11 who were undergoing bilateral adrenalectomies for palliation of metastatic carcinoma of the breast.

mendation of Harrison et al.[10] that the beta adrenergic blocker, propranolol, should be used in preparation for surgery only for specific indications (*i.e.*, HR greater than 140/min, a history of arrhythmia, persistent ventricular extrasystoles, or a pure E secreting tumor). We have not found it necessary to routinely give blood transfusions in the preoperative period.

Despite an abundance of literature, there remains some controversy concerning the most suitable anesthetic agents for the resection of pheos. Crout and Brown[5] found methoxyflurane a useful anesthetic in 16 operations for pheos, but because of its potential nephrotoxicity, this agent is seldom used now.[18] Halothane has also been used successfully for the resection of pheos. Data from one patient with a pheo suggested that halothane anesthesia maintained blood pressure within physiologic limits by suppression of circulating catecholamine concentration.[7] Halothane, however, may sensitize the ventricular myocardium to the irritative effects of epinephrine.[14] In one series, 13 of 17 patients undergoing resection of a pheo with halothane anesthesia developed ventricular arrhythmias.[4]

Our experience with this series of patients confirms the reports of other groups that enflurane is an excellent anesthetic agent for the resection of pheos.[13,15,21] Although enflurane does not suppress catecholamine secretion from pheos, it does not stimulate such secretion, and in contrast to other anesthetics, does not increase myocardial sensitivity to exogenous epinephrine.[14] Patient 1 had a transient episode of nodal tachycardia; none of the other patients developed any significant ventricular arrhythmias during enflurane anesthesia.

Since its introduction for the treatment of pheos in 1949, intravenous injections of phentolamine have been the most reliable way to control the hypertensive episodes that occur during the surgical manipulation of pheos.[8] However, in addition to its alpha-adrenergic antagonism, phentolamine has three less desirable side effects.[27] It has a histamine-like action that can result in peripheral vasodilatation or stimulation of gastric acid secretion; it stimulates the motility of the gastrointestinal tract; and it is a cardiac stimulant. The latter effect can result in tachycardia, arrhythmias and anginal pain.

Sodium nitroprusside is widely used as a rapidly acting antihypertensive agent that is useful in the management of a variety of hypertensive problems, such as hypertensive encephalopathy. As early as 1963, nitroprusside was used for the intraoperative management of a pheo patient who became resistant to the effects of phentolamine.[20] In more recent studies, phentolamine has remained the agent of choice for the intraoperative management of pheos.[6] However, if a patient develops tachyphylaxis to phentolamine, nitroprusside is substituted.[6]

After resection of their pheos, none of the patients in our series had refractory hypotension that necessitated prolonged infusion of vasopressor agents. This was probably due to a number of factors. During the preoperative period, the patients received DBZ; DBZ tends to correct the contracted blood volume in patients with pheos. During the intraoperative period, the patients received appropriate fluid replacement to maintain their circulating blood volumes, and with the exception of patient 1, they received nitroprusside rather than phentolamine to rapidly correct hypertensive episodes. The effect of nitroprusside is rapidly dissipated when its administration is discontinued. In contrast, the antihypertensive effect of phentolamine persists from 30 to 60 minutes after its administration.[27] This could lead to hypotension after the pheo is removed. In our opinion, nitroprusside infusion may be the agent of choice for the control of hypertensive episodes during resection of pheochromocytomas.

Acknowledgments

We thank Mrs. Lea B. Foster for her technical assistance, Mrs. Kathleen A. Preddy for her secretarial assistance, and Mr. Donald Powell for his excellent illustrations.

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Hollister loop ostomy method

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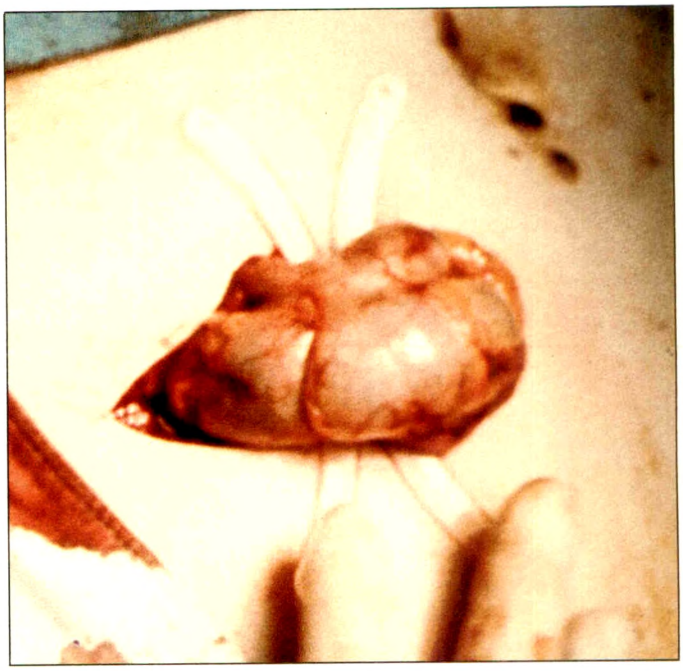
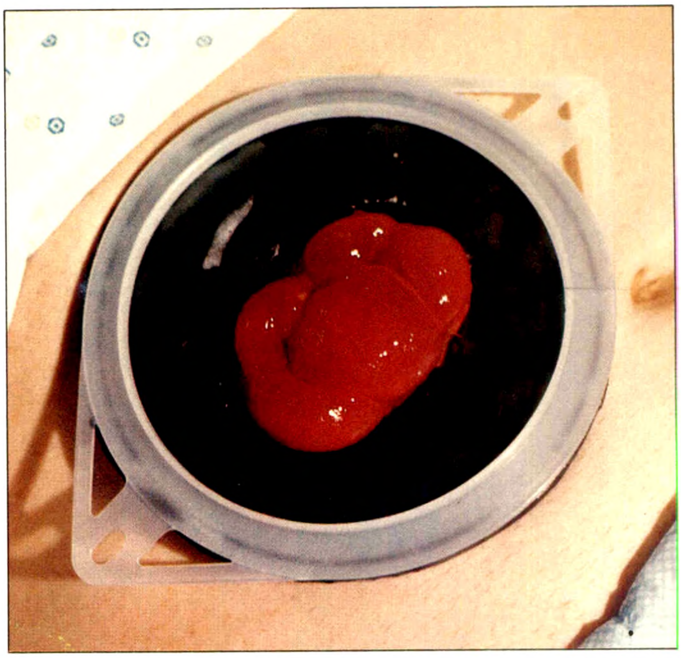
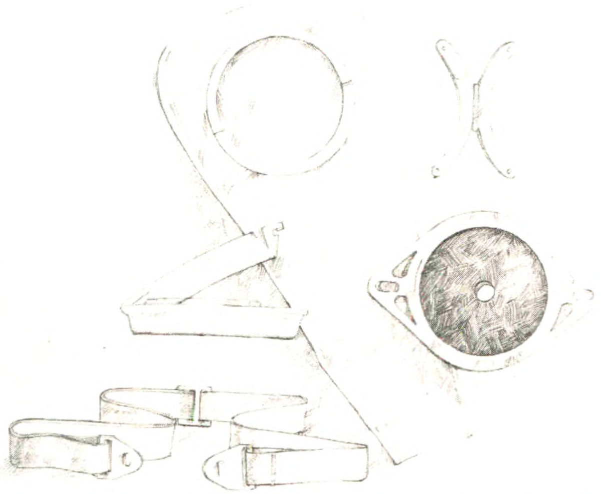


Replacing the traditional glass or plastic rod with the Hollister method can vastly simplify the management of a transverse colostomy.

The typical rod-supported stoma is practically impossible to fit with a secure drainage appliance; odor and soiled bedclothes are probable and skin irritation is likely. The Hollister method uses a unique *folding* colon support—the Loop Ostomy Bridge— that *lies flat*. This offers a major advantage over conventional loop procedures: ability to seal an appliance firmly to the skin. The Hollister karaya gasket (photo) is trimmed to fit the stoma and laid down over the bridge—hugging the skin and isolating it from fecal discharge. An odorproof pouch (illustration below) secures the drainage yet leaves the stoma visible and accessible.

To minimize the mess—and hazard—of fecal spillage, you can place the skin-protecting gasket *before* the stoma is matured.





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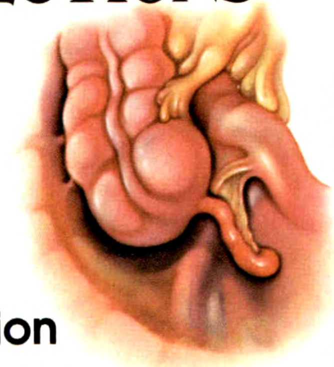
THE BIPHASIC NATURE OF SERIOUS INTRA-ABDOMINAL/PELVIC INFECTIONS



Introduction

The biphasic clinical nature of serious intra-abdominal and female pelvic infections may be related to sequential dominance first of aerobes and then of anaerobes. Antimicrobial coverage of both aerobes and anaerobes should be considered during all stages of serious intra-abdominal and female pelvic infections.

The majority of these infections are polymicrobial. During the early, toxic phase, aerobes are

Acute Phase:
Peritoneal Response

Peritoneal contamination with polymicrobial (aerobic and anaerobic) flora from the bowel or vagina may occur during surgery or as a result of trauma, septic abortion, or perforating diseases such as appendicitis.

Clinical signs in the acute phase include increasing abdominal tenderness and fever. Bacteremia, which may progress to septic shock, occurs fairly frequently. In female pelvic infections, bacteremia and septic pelvic thrombophlebitis are always a threat because of the rich vasculature of the female pelvis.

Initially, antimicrobial therapy directed against aerobes such as *Escherichia coli* often results in defervescence and clinical improvement. Failure of the patient to respond or recurrence of symptoms may indicate anaerobic involvement. *B. fragilis* is the anaerobe most frequently isolated in patients with intra-abdominal sepsis or serious female pelvic infections.

Late Phase:
Peritoneal Response

The clinical course may progress to walling off of the infection and subsequent abscess formation. These collections of pus can be located intraperitoneally, retroperitoneally, or within the viscera.

Progression from peritonitis to abscess formation may be an insidious process or may be marked by sudden deterioration of the patient who had been recovering. At this point, failure to respond to appropriate antibiotic therapy should alert the clinician to the possibility of intra-abdominal or pelvic abscess formation and

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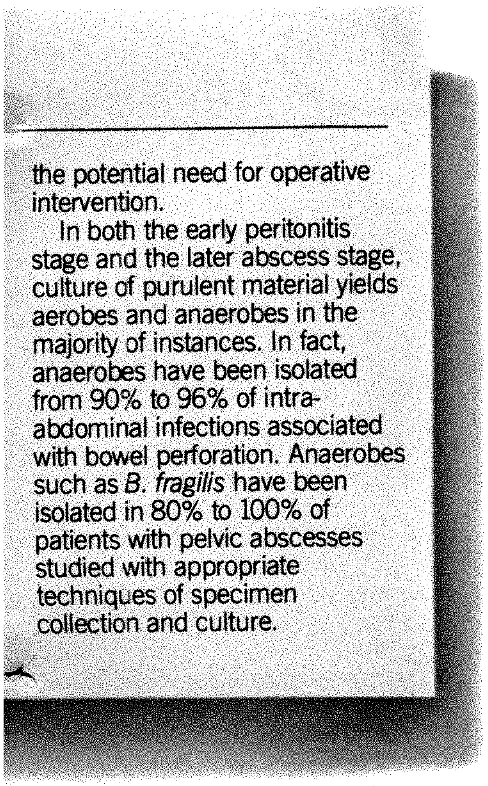
generally the dominant pathogens; the coexistent anaerobes may contribute to the clinical picture. In the patient who progresses to the late phase and develops an abscess, anaerobes (especially *Bacteroides fragilis*) are the dominant isolates.



the potential need for operative intervention.

In both the early peritonitis stage and the later abscess stage, culture of purulent material yields aerobes and anaerobes in the majority of instances. In fact, anaerobes have been isolated from 90% to 96% of intra-abdominal infections associated with bowel perforation. Anaerobes such as *B. fragilis* have been isolated in 80% to 100% of patients with pelvic abscesses studied with appropriate techniques of specimen collection and culture.

For information about one antibiotic to consider in treating serious infections due to anaerobic pathogens, please turn the page.

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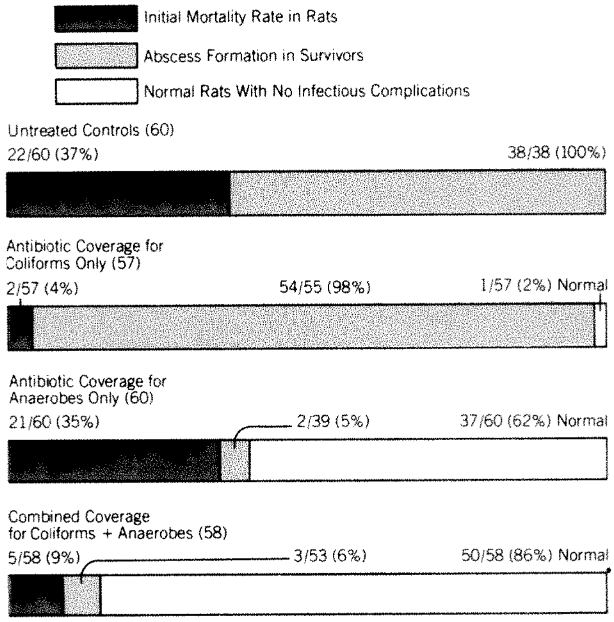
INDUCED PERITONEAL SOILAGE

The sequence of events that follow experimental induction of peritoneal soilage in rats parallels the biphasic course of this disease. Although animal data cannot be directly applied to humans, this model helps explain the pathogenesis.

A standardized inoculum of rat colonic contents containing both aerobic and anaerobic organisms was implanted into the peritoneal cavity of male Wistar rats. The animals were observed for response and survivors were sacrificed after ten days. The rats developed a two-stage disease: initial, acute peritonitis and later, intra-abdominal abscesses. Mortality and progression of these stages varied sharply with antimicrobial coverage for aerobes, anaerobes, or both.



In this study, coliform organisms appeared to be responsible for the early mortality associated with fecal peritonitis, whereas *B. fragilis* and other anaerobes were associated with later abscess formation.

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THERAPEUTIC CONSIDERATIONS...

Anaerobic activity

Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal and female pelvic infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection; serious lower respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; and serious skin and soft-tissue infections caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, in vitro dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should

consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Indications include: serious lower respiratory tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances, the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible in vitro and were successfully eradicated from the clinical lesions.

Other therapeutic considerations

1. Cleocin PO_4 (clindamycin phosphate injection) is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section of the brief summary on the following page.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

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*Clostridia are more resistant than most anaerobes to clindamycin. Some species, eg, *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro.* Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

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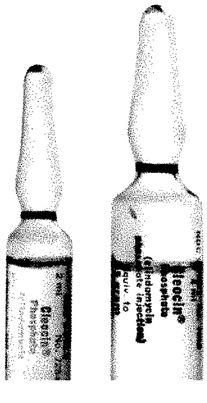

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Postoperative Pneumoperitoneum: an Unusual Etiology

MOISES TENEMBAUM, M.D., JOEL J. BAUER, M.D., IRWIN M. GELERNT, M.D.,
ISADORE KREEL, M.D., ARTHUR H. AUFSES, JR., M.D.

Although postoperative pneumoperitoneum is a common finding, it is particularly disturbing when there is an increase in the amount of postoperative pneumoperitoneum or when the radiographic finding of pneumoperitoneum is accompanied by such physical findings as increased abdominal tenderness, peritoneal signs or paralytic ileus. Four patients operated upon at the Mount Sinai Hospital are presented. All patients underwent abdominal surgery for treatment of some form of inflammatory bowel disease and all were receiving systemic corticosteroids in the postoperative period. Abdominal findings of tenderness, ileus and peritoneal irritation developed shortly after the removal of Penrose drains in the postoperative period. Pneumoperitoneum was confirmed by abdominal roentgenographs. The first patient in this group underwent a laparotomy with essentially negative findings other than a freely open drain tract. The subsequent three patients were managed by close observation and frequent abdominal radiographs. These three patients had contrast roentgenographic studies of the upper gastrointestinal tract to rule out perforation of a peptic ulcer, and in the patient upon whom reservoir ileostomy had been performed, a contrast study of the reservoir was performed. All patients recovered fully with this management and there were no sequelae. The mechanism for the appearance of pneumoperitoneum after removal of drains, particularly when the patient is receiving systemic corticosteroids, is discussed. Emphasis is placed on the need to consider and rule out perforation of a hollow viscus in this situation before accepting drain removal as the sole cause of postoperative pneumoperitoneum.

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THE PRESENCE OF free air in the peritoneal cavity in patients who have not had recent invasive abdominal procedures is usually indicative of a perforated hollow viscus and is almost always an indication for prompt operative intervention. The radiographic finding of air following abdominal surgery is common but not invariable; it could be demonstrated in approximately 77% of patients.[3] Some authors[1,2] have suggested that it is present in all patients after abdominal surgery.

A problem which occasionally confronts the surgeon is the roentgenographic finding of large amounts of intraperitoneal air in the postoperative patient. This finding is disturbing, particularly if abdominal roentgenographs earlier in the postoperative period have shown lesser or total absence of free air or if signs of peritonitis are present. It is imperative that perforation of a hollow intra-abdominal viscus be considered, and every effort be made to confirm or rule out this diagnosis. Several causes of pneumoperitoneum in the postoperative patient do not require operative intervention for their treatment. These entities must be considered when evaluating such a patient.

This report describes four patients in whom late massive postoperative pneumoperitoneum occurred immediately after intra-abdominal Penrose drains were removed. All four patients were receiving systemic corticosteroids for several months prior to surgery and continued to receive maintenance doses during the postoperative period.

Case Reports

Case 1. B.G., a 16-year-old boy, underwent a total protocolectomy and terminal ileostomy for chronic ulcerative colitis. The patient had been treated with 40 mg Prednisone, by mouth every other day for several months prior to surgery. The procedure was performed through a midline abdominal incision and Penrose drains were brought out through right and left lateral stab wounds. Postoperatively, the patient was given intravenous and then oral corticosteroids. The patient had an uncomplicated postoperative course until the thirteenth postoperative day when the right drain was removed. Several hours later, the patient complained of diffuse abdominal pain. The temperature was elevated to 38.6°. The abdomen was moderately distended and there was significant diffuse abdominal tenderness. Bowel sounds were present but hypoactive. The wound was clean and was healing well. Blood count revealed 37.000 white blood cells/mm^3 with a marked shift to the left. Abdominal roentgenographs showed massive pneumoperitoneum.

Four hours after the onset of the episode, with no improvement in the abdominal findings, the patient was explored with the presumed diagnosis of a perforated hollow viscus, (most likely due to peptic ulcer). Upon opening the abdomen, it was noted that, at the site where the Penrose drain had been placed, there was a straight and freely open tract. Thorough exploration of the abdominal and pelvic organs failed to reveal any other pathology to account for the free intraperitoneal air. The abdomen was lavaged and closed. The postoperative course was uncompli-

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Submitted for publication: March 8, 1978.

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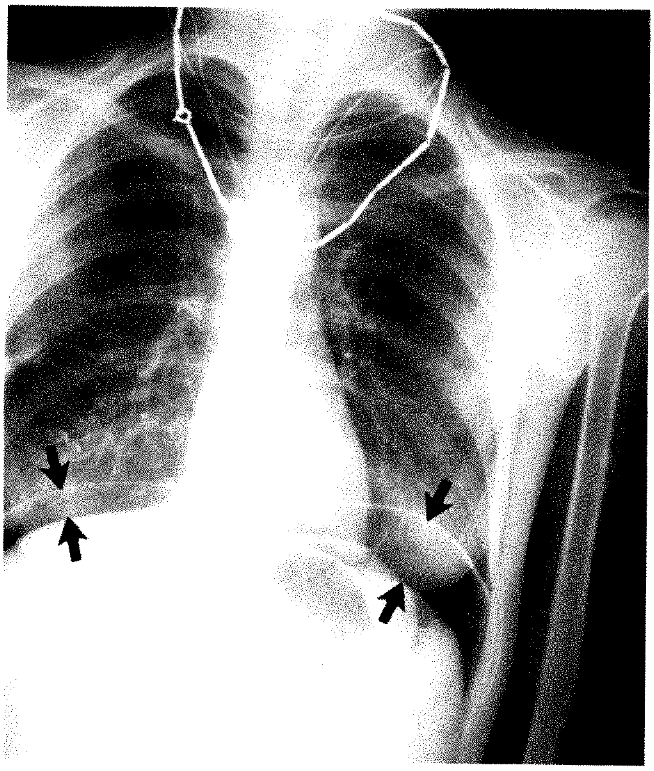

FIG. 1. Upright roentgenograph of chest demonstrating presence of free air under both hemidiaphragms (arrows).

cated and the patient was discharged on the thirty-first postoperative day.

Case 2. C.C. was a 57-year-old man with known ulcerative colitis of 15 years duration who was receiving 20 mg Prednisone per day prior to surgery. He underwent a total proctocolectomy with terminal ileostomy. The procedure was performed through a midline incision. Penrose drains were brought out through separate right and left lateral stab wounds. Intravenous and then oral corticosteroids were administered postoperatively. The postoperative course was unremarkable until the eleventh postoperative day when Penrose drains were removed from the right and left sides of the abdomen. On that evening, the patient complained of left upper quadrant abdominal pain. Temperature was elevated to 38.6°. The abdomen was soft but distended; there was mild tenderness in the left upper and lower quadrants. There was no guarding or rebound tenderness. The ileostomy output had ceased and bowel sounds were not audible.

Abdominal roentgenographs showed large amounts of free air under both hemidiaphragms and air-fluid levels in the small bowel. Intravenous fluids and antibiotics were administered. An upper gastrointestinal x-ray using Gastrografin® failed to reveal an ulcer or perforation. During the next few days, the abdomen became less distended and the tenderness subsided. On the fifteenth postoperative day, oral feedings were reinstituted. The amount of free air gradually decreased and on the twenty-fifth postoperative day he was discharged in good condition.

Case 3. R.R., an 18-year-old woman with a three year history of chronic ulcerative colitis, underwent an elective total proctocolectomy and continent reservoir ileostomy. She had been receiving methylprednisolone for several months prior to surgery. The procedure was performed through a midline incision. Penrose drains were brought out through separate right and left lateral stab wounds. Maintenance corticosteroids were administered intravenously, and then orally during the postoperative period. The postoperative course was uneventful until the fourteenth postoperative day when the patient felt very weak and had diffuse abdominal pain. This occurred approximately three hours after one left sided drain was removed. The rectal temperature was 36.7^{c}. The abdomen was soft with very mild left upper quadrant tenderness. There were no peritoneal signs. Bowel sounds were present and the ileostomy was functioning. The wound was clean and healing well.

Abdominal roentgenographs revealed large amounts of free air under the left hemidiaphragm (Fig. 1). A Gastrografin upper gastrointestinal series (Fig. 2) and a contrast study of the ileal reservoir (Fig. 3) were performed. These studies failed to reveal extravasation from either the upper gastrointestinal tract or the reservoir ileostomy. It was assumed that the free air was secondary to the removal of the drains. Oral intake was stopped and intravenous fluids instituted. The ileostomy continued to function normally.

On the seventeenth postoperative day the patient was completely asymptomatic. Two days later, oral intake was reinstituted. X-rays showed a gradual decrease in the amount of air and she was discharged on the twenty-eighth postoperative day in very good condition.

Case 4. C.M., a 25-year-old woman, underwent a subtotal colectomy and ileostomy for granulomatous ileocolitis. The patient had been receiving 20 mg/day Prednisone prior to operation. The sigmoid stump was closed with three layers of sutures, and Penrose drains were brought out through a stab wound in the left

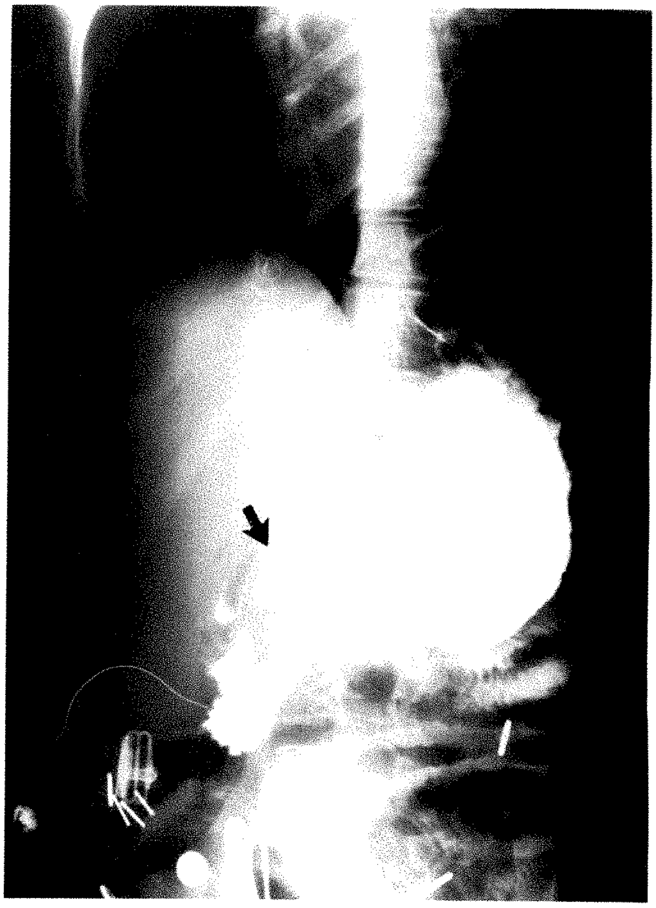

FIG. 2. Upper gastrointestinal series using gastrografin which demonstrates no extravasation from stomach or duodenum.

lower quadrant. The patient received maintenance corticosteroids postoperatively.

The postoperative course was uneventful until the tenth postoperative day when the last drain was removed. That afternoon, the patient began to complain of diffuse abdominal discomfort and bilateral shoulder pain when standing. Physical examination revealed the patient to be in no acute distress. There was mild abdominal distension and diffuse tympany. The wound was clean and well healed. There was no tenderness and the ileostomy stoma was functioning normally. Vital signs were all normal.

Abdominal x-rays revealed massive pneumoperitoneum. Upper gastrointestinal series using Gastrografin revealed no extravasation of contrast material. The patient was placed on intravenous fluids and antibiotics, and oral feedings were stopped. Her abdomen became less distended and her ileostomy continued to function normally. After 48 hours, oral feedings were reinstituted. X-rays showed a gradual decrease in the amount of free air, and the patient was discharged five days after the episode occurred.

Discussion

Postoperative pneumoperitoneum is a common finding. Its incidence ranges between 58 and 77% following intra-abdominal operations.[3,5] Any loss of the integrity of the peritoneum including small and transient openings as in inguinal herniorrhaphies or stab wounds may result in a pneumoperitoneum.[7] Postoperative intraperitoneal air may be present for a variable period of time after operation. The duration of the pneumoperitoneum is proportional to the amount of air trapped at the time of abdominal closure. From 100 to 500 cc of air may persist for approximately one week before complete absorption occurs. An average postoperative pneumoperitoneum of 500 to 1000 cc may last for approximately ten days.[3] Wiot[14] presented a case in which absorption was not complete until the thirty-eighth postoperative day.

The presence of what appears to be free air in the subdiaphragmatic space may, in fact, be a subdiaphragmatic abscess with an air fluid level. In addition to the pneumoperitoneum seen postoperatively and that associated with perforation of hollow organs, pneumoperitoneum has also been reported in association with the use of mechanical ventilatory support,[12] especially when positive end expiratory pressure (PEEP) is used.[12,8] It has also been reported following abdominal paracentesis and peritoneal dialysis.[6]

At least three cases of free intraperitoneal air entering through drain tracts have been recorded prior to this report.[5,10,4] The association of pneumoperitoneum with the removal of intra-abdominal drains and the chronic administration of steroids, as in our four patients, has not been previously reported.

It is interesting that all four patients presented in this report were symptomatic, and all complained of abdominal pain to some degree. Three of the four patients were distended with varying degrees of paralytic ileus. The temperature was elevated in two of them.

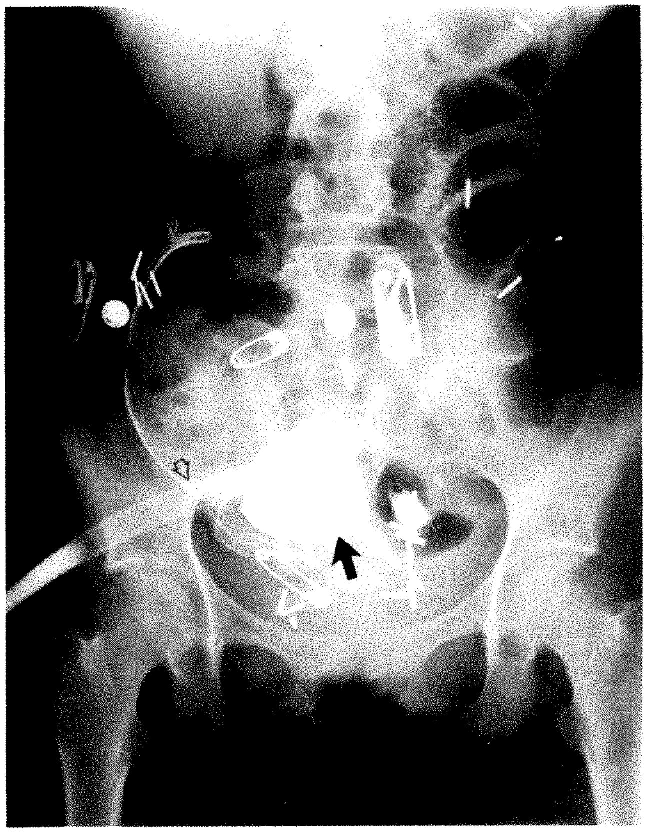

FIG. 3. Contrast study of ileal reservoir which demonstrates no extravasation (hollow arrow denotes catheter in reservoir).

The four patients reported were all receiving large doses of maintenance corticosteroids postoperatively. It is well known that the anti-inflammatory corticosteroids decrease the rate of healing of surgical wounds.[11] The inhibitory effect on wound healing occurs especially when the corticosteroids are given in moderately large doses and within the first two or three days after surgery[13] as was the case in our four patients. Corticosteroids will delay the appearance of almost all elements of wound healing. If steroids are instituted later in the postoperative period (four days or more after surgery), the effect on the healing process will be negligible. Anti-inflammatory steroids act by inhibiting the inflammatory phase of the healing process. The action can be explained in part by the effect that steroids have on lysosomal physiology. They increase the integrity of the lysosome,[9] whose enzymes are known to have a prominent role in the inflammatory process.

Drains are usually sealed off from the peritoneal cavity in a matter of hours or days following their placement.[5] When they are removed, the presence of a fibrinous response and the fact that stab wounds are obliquely placed through the tissue layers, usually facilitate almost immediate closure of the drain tracts. In the cases presented in this report, it is likely that by inhibiting the fibrinous and inflammatory response, the corticosteroids prevented the normal sealing of the drain tracts from the free peritoneal cavity or its subsequent obliteration when the drains were removed.

When a postoperative patient develops abdominal pain and findings consistent with pneumoperitoneum, the burden is upon the surgeon to prove that perforation of a hollow viscus has not occurred. This is especially true in patients receiving corticosteroids where perforation of peptic ulcers, colonic diverticula and dehiscence of anastomoses is more common. It would be a gross error to assume that the pneumoperitoneum is secondary to drain removal before excluding the diagnosis of a perforated viscus. In three of the four patients reported here, radiographic contrast studies of the upper gastrointestinal tract were performed. In one patient, a contrast study of the ileal reservoir was performed as well. Only in the first patient, B.G., encountered among these four was no contrast study performed, and this patient's abdomen was promptly explored.

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Postmastectomy Reconstruction

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Reconstructive surgery following mastectomy has had an increased acceptability with improved techniques and prostheses. Plastic reconstructive procedures following prophylactic mastectomy were performed in 104 patients and following mastectomy for cancer in 88 patients. Capsular contractions have not occurred with the use of a subpectoral pocket and detection of recurrent cancer is not hampered by the materials now used.

RECONSTRUCTION of the female breast following mastectomy is now receiving serious attention. Factors responsible for this include the development of better reconstructive techniques,[4] the availability of improved prosthetics and the demonstration that there are no adverse effects of such procedures on host resistance to tumor.[5] The large number of women in high risk groups who undergo prophylactic mastectomy and the number of younger patients undergoing mastectomy for cancer have come to expect such additional measures. Finally, the general acceptance of the modified radical mastectomy with preservation of the pectoral muscles has permitted a much better approach to breast contouring.

We present our experience in postmastectomy breast reconstruction acquired during the last six years. The patients are considered for presentation and discussion in three major categories (Table 1).

Prophylactic Mastectomy

Multiple factors have been identified as predictive of a high risk for developing breast cancer (Table 2). A family history of previous breast cancer is particularly important; the chances of developing breast cancer are increased three- to eight-fold depending on the pattern of family involvement.[1] In this setting we feel it critically important to remove all breast tissue—subcutaneous mastectomy cannot accomplish this.[3] Further, the nipple must be dissected of all breast and ductal tissue, including that which extends into the nipple papilla. Our technique, described below, satisfies these requirements.

Methods

General Surgical Technique

A transverse incision is made through the breast skin around the nipple and areola, extending from the anterior axillary line to the circular nipple incision and 2.0–3.0 cm medially. The nipple is excised and given to the plastic surgeon to thin while the total mastectomy is completed. The skin flaps are dissected moderately thin, making certain to remove all identifiable breast tissue with the specimen. The skin flap dissection is carried medially to the sternal area, superiorly to the clavicle, laterally and superiorly into the axilla to expose the tail of the breast, and inferiorly to below the inframammary line. If more exposure is required, both ends of the skin incision may be lengthened.

Breast removal is started by dissecting medially and inferiorly to reach the pectoralis fascia, where a plane of separation is easily created. A careful search is made around the periphery of the dissection to identify and remove all elements of breast tissue that may have been left in the wound. While the general surgeon commences a similar procedure on the opposite breast, the plastic surgeon can begin reconstructive efforts.

Plastic Surgical Technique

An incision is made at the lateral border of the pectoralis major at a level where it overlays the pectoralis minor high in the axilla. By blunt dissection, the pectoralis major can be lifted from the chest wall to produce a pocket which extends below the inframammary line, laterally beneath the anterior serratus

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Submitted for publication: March 25, 1978.

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TABLE 1. *Patient Classification*

	No. of Patients
Prophylactic mastectomy & reconstruction	104
Immediate postmastectomy & reconstruction	6
Delayed postmastectomy & reconstruction	52

TABLE 2. *Risk Factors for Breast Cancer*

- Family history
- Florid cystic disease
- Previous multiple biopsies
- Mastodynia
- Contralateral antecedent breast cancer

fascia, superiorly to the desired height of the position of the implant and medially to the sternum. In rare instances, the pectoralis muscle must be cut at the sternal insertion to provide lateral transfer of the muscle to cover the implant (Fig. 1).

A well-designed and executed surgical dissection of the pocket will provide a space bounded on all sides by adequate tissue sufficient to prevent motion and displacement of the prosthesis. A medium-sized suction catheter is brought from within this cavity through the inframammary skin for suction drainage. An appropriate sized implant (165–210 cc) is selected according to the size of the patient.

We prefer to use polyurethane foam covered gel-filled prostheses, which will not migrate easily because of the external covering. The implant is placed within the pocket, after positioning the patient's arms at her sides, and the opening into the pocket is closed. Skin closure is accomplished by either denuding the edge of the inferior flap to form a vascularized dermal flap for cushioning of the implant, or by direct tailoring and apposition of skin edges. We prefer the dermal flap, which provides more cusioning and substance over the prosthesis. The denuded dermal flap edge is sutured to the pectoralis muscle in a few areas to position it properly, and the upper flap is brought down as far inferiorly as possible to produce a low scar. The superior flap is then sutured to the epithelial edge of the inferior flap (Fig. 2).

The general surgeon has completed the opposite side by this time and the plastic surgeon now repeats the reconstructive efforts on the other side to effect bilateral symmetrical breast mounds. Ordinarily, the middle portion of the nipple is excised to remove all ductal elements from the graft.

When both nipple/areolar tissue specimens (previously removed and saved) have been thinned properly, the correct position for the nipples must be determined. The anesthesiologist can assist in accurately determining correct nipple position by making certain prior to general anesthesia that the table will tilt so that the anesthetized patient can be placed in a semi-sitting position. With the anesthetized patient semi-sitting, the plastic surgeon can identify both breast mounds and calculate the exact central nipple position. Preoperative measurements are of some value; the nipple should ordinarily be 15.0–21.0 cm from the sternal notch, depending on the stature of the patient. Predetermined measurements are not as accurate as intraoperative markings in the semisitting position. The patient is returned to a reclining position and appropriately sized round areas are denuded of epithelium at the sites where the nipple–areolar complexes have been marked. The grafts are sutured with interrupted 5-0 sutures with a tie-over bolster type dressing. No breast dressings are used; the suction drains are removed on the third or fourth postoperative day when drainage is minimal.

If vascularity of the breast flap is in question, it is best to determine this prior to developing the inferior

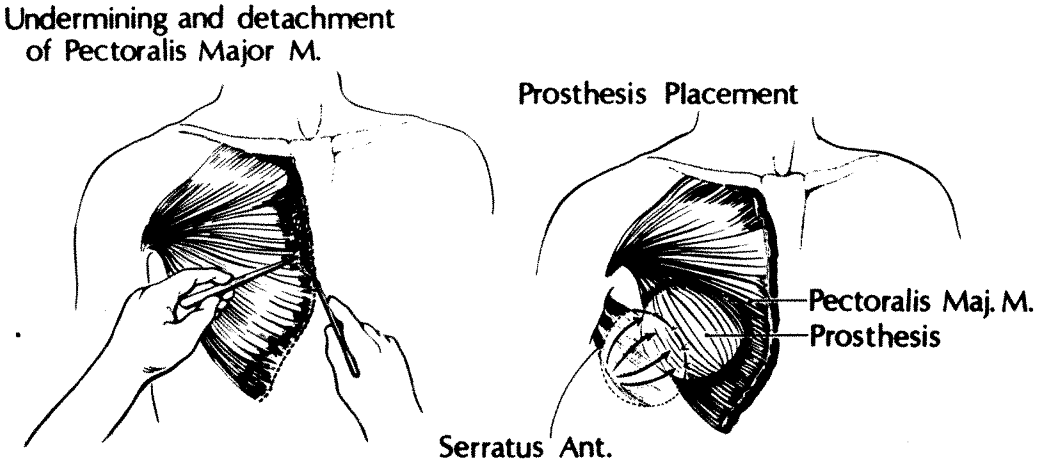


FIG. 1. Diagram of subpectoral pocket. Medial detachment is usually not necessary. The serratus fascia must be preserved.

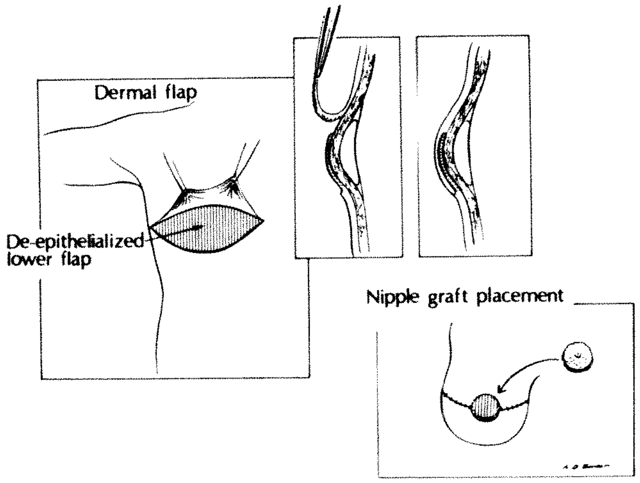


FIG. 2. Diagram of denuded dermal flap. The skin may be closed without the dermal flap.

dermal flap. If the upper flap is not viable in a certain portion, this skin should be excised and the lower flap (if viable) used for coverage. This would reduce the amount of skin available for the dermal flap. Viability of the breast flaps can best be assessed by circulation return and color of the skin and by the use of intravenous fluorescein dye and ultraviolet light. If a portion of flap does not fluoresce, we excise it, and use viable tissue for closure.

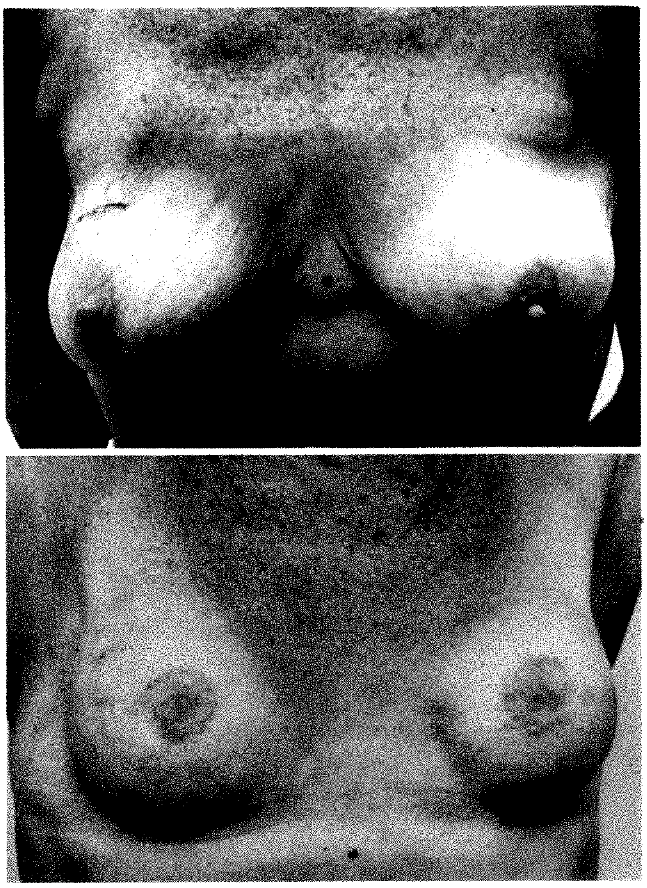
Results

Prophylactic mastectomy was performed in 104 patients; 191 breasts have been reconstructed. The indications important in deciding for such mastectomy are given in Table 3. The follow-up period has varied from one month to 10 years with an average follow-up of 3.1 years.

In the first 31 patients the prostheses were not placed subpectorally and two implants were lost. In both instances this loss resulted from small areas of skin breakdown with exposure of the prostheses. In the remaining 73 patients, with the prosthesis placed subpectorally, no prostheses have been lost, even in those situations where a modest skin loss has occurred. With subpectoral placement there has been no pain and no limitation of muscular motion. All implants placed subpectorally have remained soft and have not been distorted in shape by pectoralis pressure. The transverse skin scars remain conspicuous for a considerable time, but fade appreciably after 12 months. No early or late spherical contractures have been noted. Severe mastodynia from cystic disease, present in ten patients, was completely controlled.

TABLE 3. *Indications for Prophylactic Mastectomy*

	No. Patient	%
Carcinoma opposite breast	11	10
Florid adenosis	28	27
Giant Fibroadenomata	4	4
Incomplete subcutaneous mastectomy	7	7
Multiple above including family history	54	52
	104	

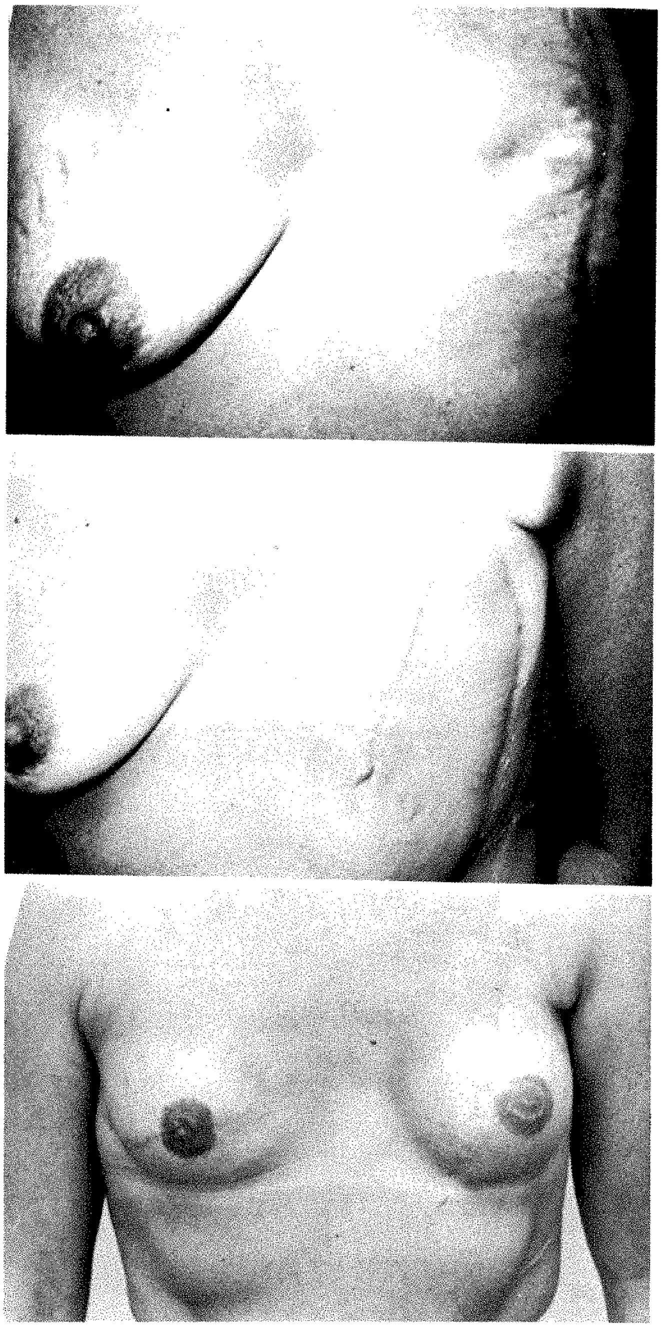


FIGS. 3a and b. Prophylactic Mastectomy—(a, top) before and (b, bottom) after. Note that with arms elevated there is neither distortion nor migration of prostheses.

No breast disease has developed or been diagnosed after our series of total mastectomies. We have sampled the margins of resection at the time of prophylactic mastectomy in 12 patients and found no residual breast tissue. This is in contrast to the biopsies after subcutaneous mastectomy, which revealed breast tissue beneath the nipple and around the periphery in all cases.[2] A patient who underwent this procedure is shown before and after the operation (Fig. 3).

Reconstruction Following Mastectomy for Cancer

The techniques employed are basically the same except that the general surgeon employs a modified



FIGS. 4a–c. Postmastectomy Reconstruction—(a, top) preoperative, (b, center) flap, and (c, bottom) delayed prosthesis.

radical mastectomy. Obviously, the patient must fulfill the usual criteria for such an operation. The prostheses can be put in place immediately in this type of situation. If extensive skin is involved, or the pectoral muscle has been invaded and must be removed, then the reconstruction may have to be staged to allow healing of properly placed skin or skin and muscle flaps. Figure 4 shows such a patient who required a skin flap for coverage and finally a delayed placement of a prosthesis.

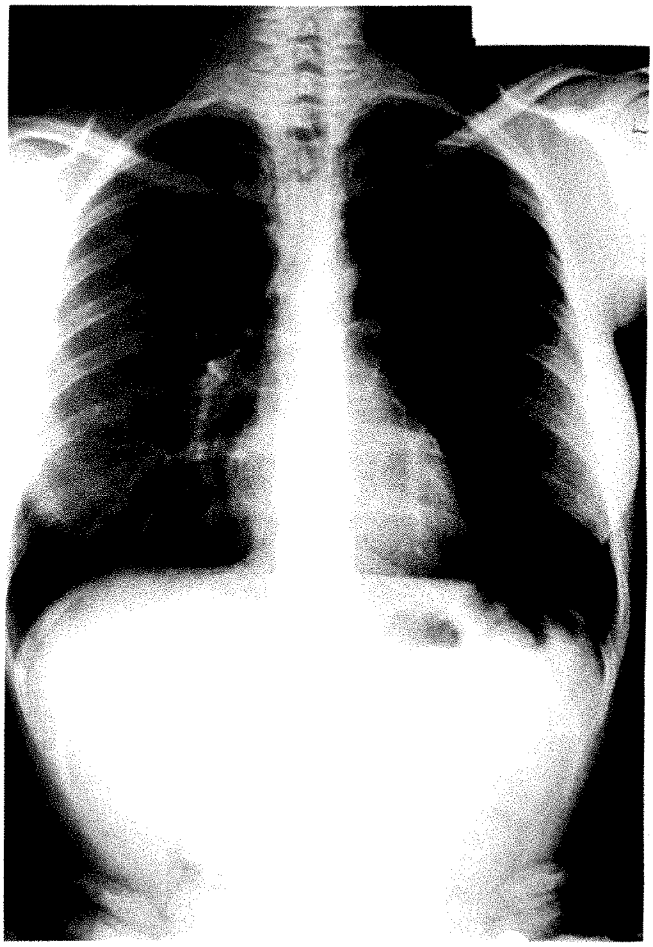


FIG. 5. Chest film in patient with bilateral silicone-gel prostheses.

Special attention must be given the nipple–areolar area in this setting. The chance of the areola or nipple being involved with tumor is only 2.0% when the nipple is clinically normal, the tumor is outside the areolar margins and the primary tumor is less than 2.0 cm in diameter; otherwise, the chance of areola or nipple involvement approaches 12%. In any case, the nipple area is thoroughly "thinned" and frozen section diagnosis obtained before replacing the nipple grafts; in larger tumors which extend into the subareolar area the nipples are not replaced and standard methods are used for nipple reconstruction.

We have operated upon 58 patients for reconstruction following mastectomy for cancer. Twenty-seven patients underwent Halsted's radical mastectomy, while 31 had a modified (Patey) procedure. The interval between mastectomy and reconstruction varied up to 12 years, averaging three years. Usually the remaining breast was removed by the previously described total mastectomy since it is a high risk organ; additionally, the symmetry and cosmetic effect is much improved where bilateral reconstruction is undertaken. Two of the 58 patients have developed recurrence. A mean of

2.8 operations were required to attain the final reconstruction.

Theoretical objections to this approach are frequently raised. We do not feel it interferes with early detection of recurrence, since the prosthesis is placed deep to the pectoral muscle and overlying changes should be readily detectable. Underlying bone changes should be as readily recognized by either bone scan or rib films. Pulmonary metastases, or any lung changes, are in no way obscured by the prostheses (Fig. 5). We have now completed animal experiments to validate the concept that the prostheses in no way divert or weaken host tumor immunity.[5]

Discussion

While the end result of prophylactic mastectomy is not as cosmetically desirable as the normal breast, this technique is believed to be preferable to either the total mastectomy without reconstruction or to the subcutaneous mastectomy. It can offer to the concerned, high risk breast cancer patient an adequate breast mound with an areolar complex, and the security that a conscientious general surgeon has removed all identifiable breast tissue. The complication rate of this operation is markedly less than that of the usual subcutaneous mastectomy reported in the literature. The capsular contractions which occur late in subcutaneous mastectomy causing distortion and firm, noncompressible, unnaturally shaped breasts over the long-term, make the total mastectomy with subpectoral implant reconstruction the preferred procedure. Time alone will tell whether this will prove to be an effective operation to prevent breast cancer. At the present, we can state that it is at least as effective as the simple mastectomy, which has been used for years as a prophylactic procedure. The standard subcutaneous mastectomy, leaving considerable remnants of breast tissue in the patient cannot make this claim.

When breast cancer is present the reconstructive procedure can follow a standard mastectomy. The axillary dissection and even subsequently proven positive lymph nodes are no contraindication—they simply alert the surgeon to the greater risk of recurrence. The extent of skin dissection or the need to sacrifice the pectoralis muscles are the major situations necessitating a flap coverage of the mastectomy wound and delayed prosthetic placement. Similarly constituted prostheses used elsewhere in the body after malignancy have had no detrimental effects. Our own studies, to be reported elsewhere, show no impairment of lymphocyte immune functions in a rat model where prostheses were placed after breast tumor excision.[2]

Enthusiastic attempts to restore patients cosmetically should now be viewed as part of the total approach to patient rehabilitation. Techniques and material now available make this possible. Physician awareness of these procedures, as well as their limitations are mandated by increasing patient demands for more acceptable results following mastectomy.

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Muscle Blood Flow Following Thermal Injury

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Peripheral circulation is markedly increased during the hyperdynamic–hypermetabolic phase of thermal injury and appears to be directed primarily to the burn wound. To determine whether any portion of this extra blood flow reaches another major peripheral vascular bed, blood flow in the tibialis anterior muscle of the lower leg was measured by ^{133}Xe clearance in ten hemodynamically stable, nonseptic burn patients (mean burn size = 42.5% total body surface) and five control subjects. Muscle blood flow was 3.52 ± 0.26 ml/100 g·min (mean ± S.E.M.) in these patients and 3.29 ± 0.24 in controls, indicating that resting muscle perfusion was unaffected by the extent of total body surface injury, size of leg burn, or elevated rectal temperature (38.2 ± 0.2°C) of the patients. These results confirm the interpretations of previous studies suggesting that most of the increased peripheral blood flow following thermal injury is directed to the surface wound. Local and systemic factors responsible for the maintenance of muscle perfusion in the face of alterations in muscle metabolism following thermal injury are discussed.

PERIPHERAL BLOOD FLOW is markedly increased during the hyperdynamic–hypermetabolic phase of thermal injury.[2,6,16] Direct measurements of total leg blood flow demonstrated that perfusion is essentially normal in uninjured limbs of burn patients but rises in a curvilinear fashion with the extent of local leg burn.[2] While this finding suggests that peripheral blood flow is wound-directed, these whole-leg measurements do not permit assessment of the distribution of blood flow among the various limb components. The present study was designed to measure muscle blood flow in the legs of burned patients and relate this component of total limb perfusion to the extent of total body injury, size of burn on that leg, and central body temperature of the patient.

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Materials and Methods

Subjects

Muscle blood flow was determined in ten burn patients (mean burn size = 42.5% total body surface, range 25.5–82%) and five normal controls. Since burn shock and the presence of a constrictive eschar or systemic "sepsis" has been shown to have a marked effect on muscle perfusion,[5,12] all resuscitated patients were studied six to 28 days postinjury when such complications were not present. Patients were free of any pre-existing disease prior to injury; normotensive and hemodynamically stable, and in a normal state of hydration with an hematocrit above 33 and without abnormalities in serum electrolyte concentration, osmolality, or pH. Blood cultures, obtained on all patients before and after the study, were negative. Burn wounds were treated by the standard open method utilizing either topical application of silver sulfadiazine cream (Silvadene®, Marion Laboratory, Inc., Kansas City, Mo.) or 11% mafenide acetate (Sulfamylon®, Winthrop Laboratories, New York).

All subjects were confined to bed for a minimum of one hour prior to muscle blood flow measurements. The actual studies took place in the Nuclear Medicine Clinic of the hospital where the ambient temperature was 25–27°. Since this was slightly below thermal neutrality for resting burned patients,[17] patient comfort was achieved by covering them with light cotton blankets. All subjects rested supine throughout the 20–30-minute study. Only those patients who rested quietly during the actual test, without any leg and/or foot movements, were included in this study.

Muscle Blood Flow Determination

Radioactive xenon gas (^{133}Xe) was dissolved in sterile 0.9% NaCl solution to a concentration of 0.5–1.0 mc/

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ml, and 0.1–0.2 ml of this solution was injected 1–2 cm into the tibialis anterior muscle through a 25 gauge hypodermic needle. The disappearance of ^{133}Xe was monitored for 20–30 minutes postinjection by a collimated scintillation probe placed directly over the injection site. Simultaneous measurements were performed on both legs in four control subjects and five patients. Muscle blood flow (MBF) was calculated from the tangent to the logarithmic curve of ^{133}Xe washout as described by Lassen, et al.[9]

$$\text{MBF (ml/100 g muscle}\cdot\text{min)} = \tau \cdot 100 \cdot \frac{-dQ/dt}{Q(t)}$$

where τ is the partition coefficient for ^{133}Xe (amount of tracer in one gram of tissue/amount of tracer in one ml blood) and

$$\frac{-dQ/dt}{Q(t)}$$

describes the clearance rate of ^{133}Xe relative to the amount present at time t; 0.70 was the value utilized for τ in both control subjects and patients.

Results

Resting skeletal muscle blood flow was essentially normal in this group of ten burn patients: 3.52 ± 0.26 ml/100 g·min (mean ± S.E.M.) as compared to 3.29 ± 0.24 in controls (Table 1). Muscle blood flow was, therefore, unrelated to the size of total body surface injury ($r^2 = 0.02$), extent of local limb injury ($r^2 = 0.004$) or rectal temperature ($r^2 = 0.27$) of the patient. The absence of a local burn effect on muscle perfusion was particularly evident from simultaneous measurements in patient 6, for this subject maintained comparable levels of muscle blood flow in both legs despite marked differences in the extent of limb injury (Table 1).

Discussion

These muscle blood flow calculations in burned patients were based on the assumption that τ, the par-

TABLE 1. *Muscle Blood Flow and Rectal Temperature of Controls and Burn Patients*

Subject*	Age (Years)	Weight (kg)	PBD Studied	% TBS Burn	% LS Burn	MBF (ml/100 g·min)	T_{re} (°C)
Controls							
1a	36	79.5				2.76	37.2
b						2.89	37.2
c						2.17	37.2
d						2.87	
2a	25	75.0				4.78	37.0
b						3.23	37.6
c						4.29	
3	30	81.8				3.16	36.8
4a	26	75.0				3.52	37.3
b						3.99	
5a	29	65.9				2.04	36.9
b						3.77	
Mean	29	75.4				3.29	37.2
± S.E.M.						± 0.24	± 0.1
Patients*							
6a	47	82	13	25.5	7.5	2.42	37.8
b					70	2.50	
7	46	108	10	27	0	3.25	37.9
8	22	52.7	8	33	10	2.60	38.7
9a	19	72.3	12	37	15	5.94	39.0
b					20	4.89	
10a	34	86	28	38	15	2.51	39.4
b					15	4.65	
11	48	73.6	11	40	62.5	3.20	38.1
12a	18	72.7	8	40	10	2.94	38.0
b					25	2.84	
13	27	72.6	6	49.5	50	3.94	38.3
14	22	65.9	20	51.5	40	4.10	39.2
15a	19	58.6	13	82	77.5	3.28	39.0
b					77.5	3.70	
Mean	30	74.4	13	42.5	33	3.52	38.12
± S.E.M.						± 0.26	± 0.2

* 1cd, 2bc, 4ab, 5ab, 6ab, 9ab, 10ab, 12ab, and 15ab are simultaneous measurements in both legs. PBD—Postburn day: % TBS = % Total body surface; % LS = % leg surface. MBF = Muscle blood flow; T_{re} = Rectal Temperature.

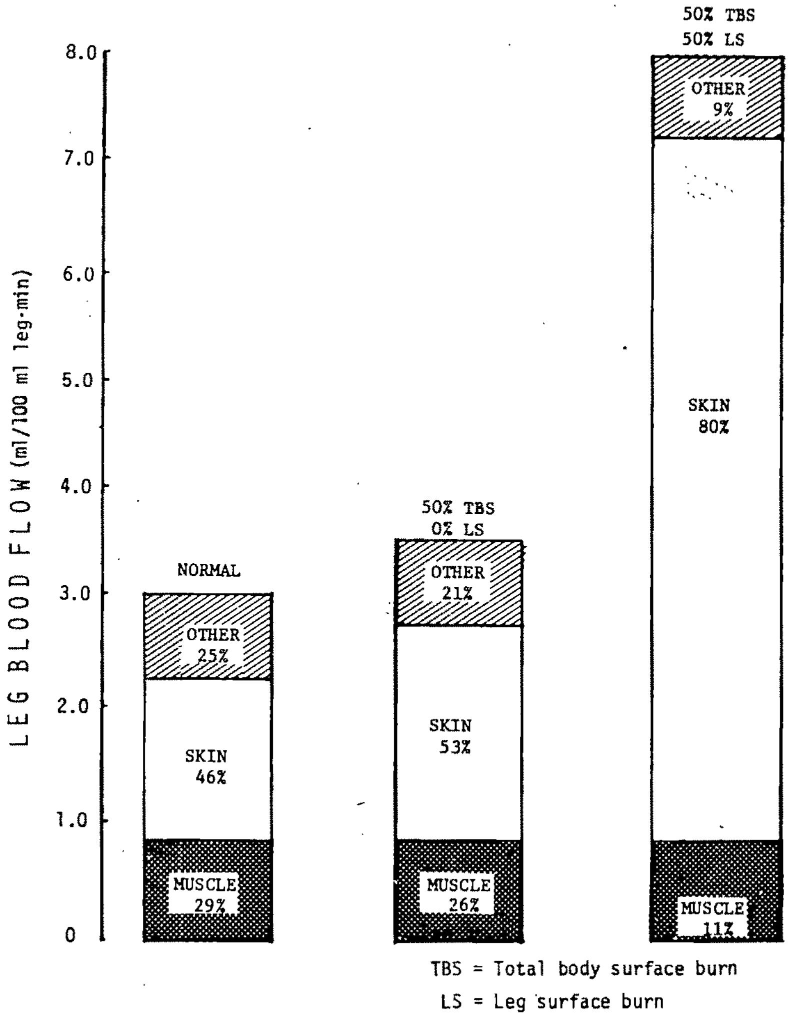

FIG. 1. Distribution of leg blood flow following thermal injury.

tition coefficient for ^{133}Xe, was unchanged in traumatized individuals. This assumption rests on the fact that, while possible changes in muscle and blood composition which occur following thermal injury may affect the relative solubility of this lipophilic tracer, these alterations are potentially offsetting and therefore do not appreciably alter τ. For example, a one gram drop in hemoglobin concentration will increase τ by 2%, but the probable reduction in tissue fat content and elevation in muscle water content would decrease τ.[13] Patient hemoglobin values averaged 13.2 g/100 ml as compared with 14.1 g/100 ml for controls. Recalculating the blood flow to compensate for only the altered hemoglobin values by increasing τ by 2–6% did not increase the calculated muscle blood flow values in patients significantly above normal. Therefore, the greatest possible difference in τ between these two groups was not of sufficient magnitude to affect data interpretation.

The results of this study, then, clearly indicate that neither the extent or location of a thermal injury has any net effect on resting muscle perfusion. The predicted normal values for muscle blood flow range between 2–4 ml/100 g tissue·min since skeletal muscle represents 40–45% of the total body mass and receives 15–20% of the cardiac output in resting noninjured man. Average muscle blood flow in this group of burn patients was within these predicted limits, equal to that of control subjects and comparable to normal values reported by others,[1,12] using the same measurement approach. Therefore, unlike total limb perfusion, which varies with the extent of local injury,[2] muscle blood flow is unrelated to the size of leg burn. These results confirm the interpretations of previous studies[2,18] which suggested that most of the increased peripheral blood flow following thermal injury was directed to the surface wound.

These peripheral blood flow measurements in burn patients make it possible to characterize the shift in limb perfusion following thermal injury (Fig. 1). Stolwijk[14] has partitioned resting leg blood flow as follows: 29% to muscle, 46% to skin, and 25% to the remainder. Assuming that there is little or no change in muscle, fat, or bone perfusion, blood flow to the skin of an unburned leg, in a typical patient with a 50% total body surface burn, increases by no more than 7% above normal.[2] Since this typical patient is febrile, with a rectal temperature ranging between 38–39°, the limited increase in superficial blood flow to the uninjured skin reflects appropriate cutaneous vasoconstriction for the generation and maintenance of a fever. This degree of hyperthermia in normal subjects, for example, would result in a five- to six-fold increase in cutaneous blood flow but would have no apparent effect on resting skeletal muscle perfusion.[10] If this same burn patient (Fig. 1) had a wound covering 50% of the leg, limb blood flow would approach 8 ml/100 ml leg volume per minute.[2] Since the size of limb burn has no effect on resting skeletal muscle blood flow, 80% of total leg flow in this patient is directed to the surface, with most of it going to the burn wound.

Are the present findings of normal muscle blood flow consistent with information available on muscle metabolism in burn patients? Previous studies[16] have demonstrated that leg oxygen consumption ($\dot{V}_{O_2}$) may increase up to 90% in resting, nonshivering burn patients. A major portion of this extra $\dot{V}_{O_2}$ must occur in skeletal muscle since 1) this tissue compartment makes up most of the limb's mass, 2) metabolic requirements of uninjured skin are minimal, and 3) the surface wound relies primarily on anaerobic glycolysis.[18] It is well established that a close relationship exists between muscle $\dot{V}_{O_2}$ and blood flow in working muscles of normal man[4,11] or resting muscles in hyperthyroid patients.[8] These findings in burn patients suggest that muscle $\dot{V}_{O_2}$ is not associated with increases in tissue perfusion.

Normal muscle circulation in the face of increased metabolic activity may be explained by the presence of competing systemic vasoconstrictor influences. Increased sympathetic activity and high levels of circulating catecholamines observed in burn patients[15] would provide a vasoconstrictor drive on the skeletal muscle vasculature. Since the vascular bed of skeletal muscle is a major site for compensatory adjustments to systemic arterial[11] and central venous pressure changes,[4,7] such reflex vasoconstrictor drives may be active in these hyperdynamic patients with high wound blood flow. Any disparity between muscle metabolism and circulation would then reflect competition between local and systemic circulatory demands. Similar competition has been observed in the working muscle of heat stressed normal man.[10]

In addition to the elevation in resting extremity $\dot{V}_{O_2}$, proteolysis and amino acid release are increased in the limbs of these patients.[3] The accelerated flux of amino acids (especially alanine) from these muscles with normal levels of perfusion is in direct contrast to reported increases in muscle proteolysis associated with elevated muscle blood flow in "septic" surgical patients.[5] Consequently, at the present time it is difficult to establish a direct cause-and-effect relationship between muscle metabolism ($\dot{V}_{O_2}$ and proteolysis) and local blood flow in the various catabolic states of injured patients.

In summary, muscle blood flow of the lower leg was normal in hypermetabolic burn patients and muscle perfusion was not affected by the local presence of a wound, changes in body temperature, or known alterations in muscle metabolism which accompany major catabolic injury. It should be re-emphasized that these studies were performed in *resting* muscle and elevations in blood flow were observed in patients excluded from this study with demonstrable limb movement. This study illustrates that burn patients without systemic infection can achieve a level of muscle perfusion consistent with local metabolic activity while satisfying other systemic, competing demands on the circulatory system. From a clinical standpoint, increases in muscle tone or frank shivering in critically ill, injured patients increase skeletal muscle perfusion and place even greater demands on the circulation of patients who already have high obligatory blood flow to the healing wound.

Acknowledgments

The authors express their appreciation to Alton W. Baker, M.D., Chief of the Nuclear Medicine Section, Brooke Army Medical Center, Fort Sam Houston, Texas, who supplied consultative services, and Specialist-5 Thomas E. Smith, III, who provided the technical assistance which made this study possible.

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Jaundice after Renal Allotransplantation

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Of 567 patients receiving renal transplantation at the University of Minnesota between October 1967 and October 1975, 22 developed clinical jaundice. Of these 22, nine died with their initial episode of hepatitis, six died within three months of causes associated with liver malfunction, four developed evidence of chronic hepatic failure and only three totally recovered from their illness. Five had clear evidence of Australia antigen positive hepatitis B, four of cytomegalovirus hepatitis, two of herpes hominis hepatitis, one of varicella zoster hepatitis and three of hepatic failure associated with systemic bacterial and/or fungal sepsis. Two of the 22 patients were thought likely to have cytomegalovirus hepatitis though definite proof was absent and in five patients a clear-cut etiology could not be made. In many of these patients the diagnosis was confounded by the previous presence of HB_sAg antigen and the frequent occurrence of a previous or concurrent infection with cytomegalovirus. The role of various drugs including azathioprine, sulfisoxazole, chlorpromazine, acetominophen, etc., could not be established but major roles for these agents in the face of the many viral and bacterial infections present in these patients is doubted. No clear-cut therapy could be established although it appears safe to discontinue azathioprine for longer or shorter periods of time with or without substitution of cyclophosphamide without serious deterioration of renal function. The problem of hepatic failure in transplant patients is still unsolved and will require a prospective study of etiologic agents and sub-clinical hepatic dysfunction in order to establish even the first principles of clinical–pathological correlation.

HEPATIC DYSFUNCTION is seen frequently after renal transplantation.[1,4,7,8,14,18,24,30,32,45] The reported incidence depends on the criteria used to make the diagnosis and varies from 7% (four-fold elevations of transaminases or serum bilirubin greater than 2 mg%)[4,7,18,30] to 67% (two-fold abnormal dye retention).[4] Whereas most of these enzyme abnormalities are of indeterminate clinical significance,[4] a small per cent of patients progress to frank liver disease and death. Identification and early institution of therapy in these high risk patients may improve their poor prognosis.

The etiologies of liver dysfunction have been attributed to a variety of viral and/or pharmacologic agents for which the evidence is circumstantial. Questions still exist regarding the proper treatment and whether or not immunosuppressive agents[4,7,18,34,45] should be changed. This study was designed to review, in a large kidney recipient group from a single medical center, those patients who developed the more severe form of hepatic dysfunction, *i.e.* those with jaundice. In this group of 22 patients we have attempted to define the mode of clinical presentation, a useful diagnostic approach, etiologic classification and prognostic guidelines.

Materials and Methods

From October 1967 to October 1975, 567 patients received 661 renal allografts at the University of Minnesota; 271 were from cadaveric donors and 390 from living related donors. The methods of patient selection, techniques of transplantation and methods of immunosuppression have been described elsewhere.[37]

Twenty-two patients have been identified who developed clinically apparent jaundice at some time during their posttransplant course. Only patients with a serum bilirubin of 2.0 mg% or higher were selected for this study (normal range = 0.1–1.6 mg%). (Patients who demonstrated liver enzyme abnormalities without bilirubin elevation were not included.) All 22 patients were admitted to the hospital at the time of their illness. This patient group was analyzed for the clinical, biochemical, pharmacological, microbiological and histopathological aspects of their illness. All survivors have been followed (27 months to seven years) with regard to longterm survival, kidney graft function and liver function status. Detailed autopsies, including viral and bacterial cultures, were performed on 15 of the 17 patients who died. Particular attention was paid to chemical abnormalities, *i.e.*, blood urea nitrogen (BUN), creatinine, bilirubin, glutamicoxaloacetic transaminase

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Submitted for publication: November 12, 1977.

0003-4932/78/1200/0783 $00.90 © J. B. Lippincott Company

TABLE 1. *Characteristics of Icteric Transplant Patients*

Period (Inclusive)	Total Number of Transplants	Total Number of Patients	Number of Icteric Patients	M:F	Mean Age* (Range)	LRD:CAD	Transplant Number	
							1st	2nd
Oct. 1967–Oct. 1975	661	567	22 (4%)	11:11	34.3 (20–53)	11:11	19	3

* One child age 3½ years not included. M = male. F = female. LRD = living related donor. CAD = cadaver donor.

(SGOT), alkaline phosphatase, lactic-dehydrogenase (LDH) and serum protein electrophoresis. In order to gain prognostic information, liver function studies were noted at the onset of liver dysfunction, as well as the maximal level attained. Microbiological studies included standard aerobic and anaerobic bacterial cultures and fungal cultures. Serology for hepatitis B (HB_sAg) antigen was performed by both counter electrophoresis (CEP) and radioimmunoassay (RIA). Viral serology for complement fixing antibody (CF) against cytomegalovirus (CMV), herpesvirus hominis (HVH) and varicella zoster (VZ) was obtained. Viral cultures for these viruses utilized methods previously described.[33] An antibody titer $\geq$ 1:4 was considered positive and a two-fold rise of titer was considered evidence of recent viral infection. Patients were additionally grouped according to the most likely primary etiology in each case.

Results

Clinical Profile and Prognostic Significance of Clinical Factors

Age and donor source (Table 1). Among the 22 patients with clinically apparent jaundice, there were ten adult males and 11 females with a mean age of 36.0 and 32.9 years respectively. There was one male child 3.5-years-old. Nineteen patients had received one kidney transplant and three patients received two transplants. Eleven patients received kidney grafts from living related donors and 11 from cadaveric donors (Table 1) (there is a greater than 4:3 ratio of recipients of related transplants to recipients of cadaver transplants in our entire series).

Time interval, transfusion history, and renal function. In 18 of 22 patients, the duration of dialysis before transplantation was less than six months but all patients received blood transfusions either while on dialysis or in the course of their operations (bilateral nephrectomy and splenectomy and/or transplantation). The time interval between transplantation and the onset of icterus was less than six months in ten of the 22 patients (in six of ten it was less than six weeks, Tables 2–7). In 12 patients, the interval varied from 8–39 months and in one patient it was over eight years. Patients with CMV hepatitis had a shorter interval from transplant to jaundice (see below). With the exception of one patient who developed jaundice shortly after removal of a second rejected graft, almost all of 22 patients became icteric with good renal function (serum creatinine <1.5 mg/l). Seven patients had had no rejection episodes. Two patients, however, received a full course of empirical antirejection treatment in the face of chemical liver dysfunction and died two to three weeks later (one in liver failure).

Clinical presentation. The most common presenting symptoms in this group of 22 patients were fatigue (18, 81%) and anorexia (15, 68%). Pruritus was present in three and abdominal pain in three. Fever was the most common physical sign, present in 16 (73%) early; four more patients developed fever later in the course of the illness. Jaundice was present on admission in 16 (73%) and developed subsequently in the rest. Bleeding and ascites were late manifestations in five patients

TABLE 2. *Relationship of Onset of Jaundice to Time of Transplantation and Rejection Episodes*

Source of Kidney	Number of Patients	Number of Rejections/Patient	Transplant → JD Interval (Months)	Last Rejection → JD Interval (Months)	Serum Creatinine at JD		History of Liver Disease
					<2.0	>2.0	
LRD	11	0.6	Range = 1–38* (mean 13)	1–27 (6 pts)*	11	0	1
CAD	11	1.3	Range = (½–23) (mean 12)	1–9 (10 pts)	10	1†	1

LRD = living related donor. CAD = cadaver donor. JD = jaundice. *One patient developed JD at 8 years (not included). †One patient had posttransplant nephrectomy.

TABLE 3. *Hepatitis B (HB_sAg+)*

Pt #	Age/Sex/ Kidney Source	Months Posttx	HB_sAg	WBC <3000 (Early)	CMV/HVH & VZ Serology (+ > 1:4)		↑Titer $>2^2$	Viral Cultures CMV		Viral Cultures HVH		Bact. Cultures (Pathogen)		Liver Pathology (Biopsy or PM)	Outcome
					PreJD	AtJD		Clin	PM	Clin	PM	Early	Late/PM		
1	25/F/CAD	4	+	−	+/	+/	−/	+	+	−	−	−	−	Bx: cirrhosis PM: massive hepatic necrosis	CAH Death (4 yrs posttx), liver failure and CMV pneumonia
2	35/F/LRD	12	+	−	+/−	+/−	−/	−		−		−	−	ND	Death. CAH
3	41/M/CAD	12	+ ↓ −	−	+/	−/	−/	−		−		−	−	ND	CAH
4	21/M/CAD#2	8	+	−	+/−	+/−	+/−	−	ND	−	ND	−	−	PM: coarse nodular cirrhosis & CAH	CAH. Died 4 months later of unrelated causes
5	21/F/CAD#2	<1	+	+	−/−	−/−	−/−	−	−	−	−	−	+	PM: cholestasis. Centrilobular necrosis	Died of fulminant liver failure + sepsis
	Total # = 5	m̄ = 7	5/5	1/5	4/5	3/5	1/5	1/5	1/5	0/5	0/5	0/5	1/5		CAH = 4/5 Dead = 4/5

JD = jaundice. Clin = clinical. PM = postmortem. Bx = biopsy. CAD = cadaver donor. LRD = living related donor. CAH = chronic active hepatitis. ND = not done. m̄ = mean.

each. Only one patient presented with ascites. The liver was palpable in only two patients at the time of admission. There was no correlation between clinical presentation and presumed etiology.

Pre-existing liver disease. Of the 22 patients studied, only 2 (9%) had any history of pretransplantation liver disease. One (patient 1, Table 3) had clinical hepatitis (HB_sAg+) while on dialysis more than one year before transplantation. The other (patient 10, Table 5a) was HB_sAg+ before transplantation but without clinical evidence of hepatitis. His subsequent fatal sepsis and liver failure appeared to be due to CMV infection.

Concurrent infections. Many patients displayed obvious manifestations of a concurrent infectious process which preceded frank evidence of liver disease. Three patients had mucocutaneous herpesvirus disease; two had HVH Type II (H. genitalis) and one patient had VZ (patients 6–8, Table 4). Patient 17 had manifestations of candidiasis (Table 6). Patients 15–17 (Table 6) who developed liver failure secondary to bacterial sepsis had fever and various other manifestations of sepsis preceding jaundice and liver failure. Patient 19 (Table 7) developed jaundice secondary to acute recurrent pancreatitis associated with hyperparathyroidism and hypercalcemia. Thus, eight of the 22 patients had a recognizable clinical syndrome of infection predisposing their jaundice.

The role of drugs. In 15 patients (68%) the dose of azathioprine and prednisone was at regular maintenance level (2–3 mg/kg/day and at 0.25 mg/kg/day, respectively). In six patients who had received the transplant less than six weeks before their jaundice, the azathioprine dose and prednisone dose had recently been higher as previously described in our protocols.[37] Two patients received a full rejection treatment (increased prednisone dosage) just prior to or in the face of liver dysfunction.

Other potentially hepatotoxic agents noted were sulfisoxazole in all patients, alpha-methyl dopa and chlorpromazine used occasionally. Acetominophen (Tylenol) has been implicated as potentially hepatotoxic in high doses[28] and was frequently given to those patients

TABLE 4. *Herpes Simplex (HVH) and Varicella-Zoster (VZ) Hepatitis*

Pt #	Age/Sex/ Kidney Source	Months Posttx	HB_sAg	WBC <3000 (Early)	CMV/HVH & VZ Serology (+ > 1:4)		↑Titer $>2^2$	Viral Cultures CMV		Viral Cultures HVH		Bact. Cultures (Pathogen)		Liver Pathology (Biopsy or PM)	Outcome
					PreJD	AtJD		Clin	PM	Clin	PM	Early	Late/PM		
6	21/F/LRD	7 yrs	−	+	−/−	−/−	−/−	−	−	/+ blood	/+ liver	−	−	PM: submassive hepatic necrosis; H. Hominis	Death in liver failure. diffuse bleeding
7	20/F/LDR	28	−	−	+/+	+/+	*−/+			/+		−	−	ND	Alive and well
8	19/F/LRD	2	−	+	−/−	−/−	*−/+	−		/−		−	+	ND	Alive and well
	Total # = 3	−	0/3	2/3	1/3	1/3	0/3	0/3	0/3	1/3	1/3	0/3	1/3		Dead = 1/3 CAH = 0/2

* Significant rise in CMV antibody titer (1:512) two months following illness. JD = jaundice. Clin = clinical. PM = postmortem. Bx = biopsy. CAD = cadaver donor. LRD = living related donor. CAH = chronic active hepatitis. ND = not done.

TABLE 5a. *Cytomegalovirus (CMV) Hepatitis*

Pt #	Age/Sex/ Kidney Source	Months Posttx	HB_sAg	WBC <3000 (Early)	CMV/HVH & VZ Serology (+ > 1:4)			Viral Cultures CMV		Viral Cultures HVH		Bact. Cultures (Pathogen)		Liver Pathology (Biopsy or PM)	Outcome
					PreJD	AtJD	↑Titer $>2^2$	Clin	PM	Clin	PM	Early	Late/PM		
9	23/M/CAD#2	2	–	–	+/–	+/+	–/–	+	+ liver	–	–	+*	–	PM: Plasma cell and lymph infiltrate; CMV inclusions	Death from bleeding secondary to liver biopsy
10	25/M/LRD	1	+	+	–/	–/	–/	+ liver	+ liver	–	–	–	+	Bx & PM: Cholestasis; focal necrosis; CMV inclusions	Death with CMV pneumonia and respiratory failure
11	30/F/LRD	1	–	+	+/+	+/+	+/	–	+	–	–	–	+	PM: Bile stasis; fatty changes	Death of CMV; respiratory failure
12	25/M/LRD	6	–	+	+/	–/	–/	+	+	–	–	–	+	Bx & PM: Massive hepatic necrosis	Death. Acute hemorrhagic pancreatitis and hepatic failure
	Total # = 4	m̄ = 2.5	1/4	3/4	3/4	2/4	1/4	3/4	4/4	0/4	0/4	1/4	3/4		Death = 4/4

TABLE 5b. *Probable Cytomegalovirus (CMV) Hepatitis*

13	53/M/CAD	23	–	+	+/	+/+	?*	–	ND	–	ND	–	+	ND	Death of liver failure
14	3.5/M/LRD	1	–	+	ND	ND	ND	ND	ND	ND	ND	–	–	ND	Death. Varicella

* CMV antibody titer 1:256, but no recent titer available to confirm rise. JD = jaundice. Clin = clinical. PM = postmortem. Bx = biopsy. CAD = cadaver donor. LRD = living related donor. m̄ = mean. ND = not done.

with a febrile course. No patients had received isoniazid. Azathioprine and prednisone were stopped or markedly decreased with bilirubin elevation or suspected sepsis. In the survivors azathioprine was gradually restarted. In two patients (patient 15, Table 6; patient 19, Table 7; one with pseudomonas sepsis and the other with septic pancreatitis) cyclophosphamide was substituted for azathioprine shortly before death. Only one of the surviving patients was restarted on cyclophosphamide rather than azathioprine following her jaundice and this patient had chronic active hepatitis documented histologically at death.

Laboratory values. Laboratory values did not provide important information regarding the differential diagnosis of jaundice.

Serum creatinine. In 21 patients serum creatinine was ≤ 1.5 mg% (Table 2). Renal function remained essentially without change throughout the illness and in all long term survivors.

Serum bilirubin. On admission, serum bilirubin ranged from 1.4 to 11.1 mg%. The mean admission bilirubin level was 5.6 mg% in patients who subsequently died (range = 2.5–11.1 mg%) and 4.6 mg% (range = 1.4–9.2 mg%) in survivors ($p \leq 0.05$). The mean maximal bilirubin in survivors was 4.5 mg% (range = 2.1–9.2 mg%), which was significantly ($p \leq 0.05$) lower than in those patients who died of causes other than hepatic failure (mean = 13.8 mg%; range = 5.8–22 mg%) or directly as a consequence of hepatic failure (mean = 25.2 mg%, range = 16–30 mg%).

Serum glutamic oxalacetic transaminase (SGOT) (normal = 7-26 IU/l). All patients except one showed an

TABLE 6. *Liver Failure Secondary to Sepsis*

Pt #	Age/Sex/ Kidney Source	Months Posttx	HB_sAg	WBC <3000 (Early)	CMV/HVH & VZ Serology (+ > 1:4)			Viral Cultures CMV		Viral Cultures HVH		Bact. Cultures (Pathogen)		Liver Pathology (Biopsy or PM)	Outcome
					PreJD	AtJD	↑Titer $>2^2$	Clin	PM	Clin	PM	Early	Late/PM		
15	29/M/LRD	28	–	+	ND	+/	–/	+ kidney	–	–	–	+	+	Bx: Cholestasis; portal fibrosis PM: Centrilobular cholestasis	Death in 2 months of sepsis
16•	42/F/CAD	13	–	–	+/	–/	–/–	+ urine	–	–	–	+	+	PM: Fatty metamorphosis; cholestasis; no necrosis	Death of Staph. sepsis secondary to bacterial valvular infection
17	49/M/CAD	3	–	–	+/+	+/+	–/–	–	–	–	–	+	+	PM: Candidiasis; cholestasis	Death of candida + bacterial superimposed sepsis
	Total # = 3	m̄ = 14.6	0/3	1/3	2/2	2/3	0/3	2/3	0/3	0/3	0/3	3/3	3/3		Death = 3/3

JD = jaundice. Clin = clinical. PM = postmortem. Bx = biopsy. CAD = cadaver donor. LRD = living related donor. ND = not done. m̄ = mean.

TABLE 7. *Hepatitis of Undetermined Etiology*

					CMV/HVH & VZ Serology			Viral Cultures				Bact. Cultures (Pathogen)			
					(+ > 1:4)			CMV		HVH					
Pt #	Age/Sex/ Kidney Source	Months Posttx	HB_sAg	WBC <3000 (Early)	PreJD	AtJD	↑Titer $>2^2$	Clin	PM	Clin	PM	Early	Late/PM	Liver Pathology (Biopsy or PM)	Outcome
18	45/F/LRD	38	–	–	+/	+/+	–/–	–	+	+	–	–	–	PM: Massive hepatic necrosis	Death of liver failure
19	45/F/CAD	6	–	–	+/	+/	–/–	–	+ liver	–	–	–	+	Bx & PM: Centrilobular degeneration	Death due to septic pancreatitis
20	26/M/CAD	12	–	–	–/	–/	–	–	ND	–	ND	–	–	Bx: Cirrhosis and infiltrate	Alive. CAH
21	58/F/CAD	9	–	–	–/–	+/+	?*	–	ND	–	ND	–	–	ND	Alive. Normal liver enzyme
22	57/M/CAD	16	–	–	–/–	+/+	?*	–	ND	–	ND	–	–	Bx: Normal liver	Death. Crypt. meningitis. CAH. ↑bilirubin
	Total # = 5	m̄ = 16.2	0/5	0/5	2/5	4/5	0/5?	0/5	2/2	1/5	0/2	0/5	1/5		Death = 3/5 CAH = 1/2 (surv.)

* No recent titers for comparison. JD = jaundice. Clin = clinical. PM = postmortem. Bx = biopsy. CAD = cadaver donor. LRD = living related donor. ND = not done. CAH = chronic active hepatitis. m̄ = mean.

elevation of SGOT. The mean maximal value in patients who expired was 585 IU/l (range = 20–3700 IU/l) versus a mean of 268.2 IU/l (range = 120–579 IU/l) in survivors.

Alkaline phosphatase (normal = 60–220 IU/l). The initial values in the survivor group was a mean of 372 IU/l (175–864 IU/l) and in those who died 451 IU/l (175–740 IU/l). The maximal values in survivors was a mean of 584 IU/l (175–1220 IU/l) and in those who died the mean was 747 IU/l (range = 625–3402 IU/l). There were no consistent elevation patterns associated with the various etiologies.

Serum lactic dehydrogenase (LDH) (normal = 130–309 IU/l). The survivors had an initial mean of 333 IU/l (range = 90–553 IU/l) and a maximal mean of 689 IU/l (range = 590–1050 IU/l). In those patients who died, the initial mean was 670 IU/l (range = 590–1050 IU/l) and the maximal mean was 1653 IU/l (range = 570–3007 IU/l). These differences are significant ($p < 0.01$). Again, no distinction could be made as to etiology.

None of these patients were jaundiced on the basis of biliary calculi or biliary tract disease.

Analysis for Primary Etiology

Tables 3–7 summarize the bacterial, viral and pathological data we used in categorizing the patients along the lines of "most probable primary etiology" for their jaundice. Clinical and biochemical features are omitted from these tables because they seemed to be of no use in making the differential diagnosis of prognostic value. An exception to this statement is made for the time interval from transplantation to the onset of jaundice, which tended to be short (one to two months) in the "proven" cases with CMV hepatitis (Table 5). The decision to categorize these patients according to a single etiologic process based primarily on viral isolation and serological studies was difficult since most of these patients (as in 80% of the general transplant population) had evidence of prior cytomegalovirus infection. Additionally a few had positive cytomegalic cultures. The decision was usually based on the recent appearance of a viral isolate or a recent seroconversion rather than the clinical pattern though clinical factors were taken into consideration.

Viral hepatitis B (HBsAg positive hepatitis) (Table 3). Five patients were HBsAg positive at the time of jaundice; three of whom were also positive prior to transplantation. With the exception of patient 5 who became icteric and positive for HBsAg shortly after retransplantation, the mean interval from transplantation was nine months. Bacterial and cytomegalovirus infections did not appear to play important roles in the pathogenesis of the liver disease. Of the five patients, one died with the initial episode of jaundice, and two more patients died as a direct result of liver dysfunction, liver dysfunction was persistent in the other two, one of whom has died of other causes.

Herpesvirus hominis *(HVH) and* Varicella Zoster *(VZ) hepatitis (Table 4).* Three patients appeared to have hepatitis due to herpesviruses other than CMV; two patients had HVH hepatitis and one had VZ hepatitis. Patients 7 and 8 (Table 4) showed strong CMV seroconversion at two months after illness and a contribution of CMV to the hepatitis cannot be ruled out. All three patients were young females (ages 19–21 years). Patients 6 and 7 developed herpes progenitalis. Patient 6 had an acute fulminant course with systemic disease terminating in liver failure death in less than one month. Viral cultures were positive for HVH from blood and urine and massive hepatic necrosis was accompanied by typical HVH inclusions. Patient 7 recovered after a febrile illness, mild jaundice (bilirubin 3.0 mg%) and had had positive cultures for HVH for two months prior to jaundice. She seroconverted to both

HVH and CMV during this illness but CMV was never cultured.

Patient 8 developed jaundice during a febrile illness with VZ with a painful rash in a polydermatomal distribution. Seroconversion (1:512) to VZ resulted during this illness. She was treated with adenine arabinoside and temporary cessation of azathioprine and recovered without sequelae.

An important prognostic factor among these patients may be the development of strong seroconversion seen in the two patients who ultimately recovered.

Cytomegalovirus (CMV) hepatitis (Table 5a). Four patients presented with strong evidence of CMV isolation from liver tissue either antemortum or at autopsy. All had developed the viral syndrome in the first two months after transplantation. Three of the four had significant leukopenia. Serial antibody studies were available for three patients; two had complement-fixing antibodies to both CMV and HVH, all three had CF antibodies to CMV but only one patient seroconverted (1:64) at the time of illness. All four patients died. The causes of death and liver pathology are noted in Table 5a.

Suspected cytomegalovirus (CMV) hepatitis (Table 5b). Two patients are also suspected of CMV hepatitis. The first, patient 13 (Table 5b) had a nearly fatal CMV infection at two months after transplantation, at which time he seroconverted to CMV (1:4096) and recovered. Almost two years later he presented with mild renal malfunction which was treated as rejection. This was followed by severe leukopenia, jaundice and a fulminant and fatal course of liver failure. Unfortunately, viral tests and an autopsy were not performed.

The second patient was a child who developed a febrile illness with leukopenia, mild jaundice shortly after transplantation and recovered. Viral diagnostic data are not available, but CMV infection is very likely on the basis of the clinical presentation.[37] This patient subsequently died with systemic varicella infection one year later.

Jaundice secondary to bacterial or fungal sepsis (Table 6). Three patients developed jaundice secondary to fatal bacterial or fungal systemic sepsis. The diagnosis became apparent in all three based on routine culture results. Two of these three patients had evidence of presence of CMV at time of illness but CMV could not be implicated as an etiology for their jaundice or death.

Hepatitis of undetermined etiology (Table 7). This group of five patients did not present with a clearly defined etiology of jaundice. The patients tended to be in the older age group and the onset of jaundice was *not* early after transplantation. They presented with symptoms typical of hepatitis (fatigue, anorexia) but without fever. Only patient 18 presented with fever and she had pneumonitis at the time. They were free of bacterial or fungal infection; the only sepsis being predeterminal in patient 19 who died of pancreatitis and peritonitis following a negative biliary tract exploration.

The CMV viral serology was positive in four (80%) but there were no documented seroconversions or positive viral cultures during the illness or subsequently (except the virus isolated from the liver of patient 19). The liver biopsies performed were not diagnostic. Patient 22 had normal appearing liver. One patient died in fulminant liver failure. Half the survivors have evidence for chronic liver dysfunction on long-term follow-up. The liver disease in these five patients may be drug related or associated with an as yet undetermined viral agent.

Discussion

Although chemical evidence of liver dysfunction has been frequently noted (7–67%) among kidney transplant recipients,[1,4,7,8,14,18,24,30,32,34,45] we have not prospectively followed liver function studies in our patients and the true incidence of hepatic malfunction in the Minnesota series is unknown. The incidence of clinical jaundice in this retrospective study was 4%, within the range of 2–9% found by others.[1,4,8,32,34] Many factors can cause minimal or severe liver disease in transplant patients and neither the causes nor cures are readily apparent.

Most of the patients (91%) had no history of prior liver disease. The two exceptions were patients with history of positive HBsAg (one associated with clinical hepatitis). Pretransplant HBs antigenemia is not thought to carry an increased risk of posttransplant liver failure.[9,32,36] However considerable controversy remains regarding this point.[4,23,31,33,42,43]

The interval time between transplantation and development of jaundice varied widely; from less than one month to eight years. There is, however, a definite tendency for the jaundice due to CMV infection to occur earlier ($\bar{M} < 2.5$ months) than jaundice associated with other etiologies. In this regard, of a group of 23 patients, the six (25%) who developed jaundice within two months of transplantation were still receiving large doses of immunosuppressive therapy. High dose azathioprine may be related to direct hepatotoxicity[41,47] or increased susceptibility to viral hepatitis.[5,46] Two patients also succumbed to progressive liver failure after high dose steroid treatment for supposed "rejection" in the face of mild jaundice. Both had a viral component to their illness.

Ninety per cent of patients in this series had good renal function at the onset of jaundice and in those patients who survived there was no deterioration of renal function, even in patients in whom azathioprine was stopped for prolonged periods. The maintenance of renal function in the absence of immunosuppressive agents has been observed previously,[17,26] and might be of therapeutic importance especially in the management of infectious liver disease.

The initial clinical syndrome was not diagnostic as to etiology with the exception of the following: 1) mucocutaneous manifestations of HVH and VZ preceded the evidence for liver involvement by two weeks or longer, and 2) prolonged, spiking fever (>101°F), less than 60 days after transplantation is strongly suggestive for CMV infection. Blood chemistries were not discriminative in terms of the differential diagnosis or prognosis.[1,24]

Other diagnostic measures such as liver scans and cholangiography have not been helpful. Retrograde cannulations and exploratory laparotomy have all been negative. In none of these patients was obstructive biliary calculus disease encountered, in agreement with others' series.[1,4,7,8,14,18,24,30,32,45] For this reason extensive diagnostic studies to rule out obstructive etiologies are not warranted.

We have not demonstrated the usefulness of liver biopsy in our series; no changes were made in either diagnosis or treatment on the basis of histologic findings at biopsy. This probably reflects the fact that most were performed late in the clinical course. In contrast, other transplant groups have found biopsy useful, both in planning treatment (*e.g.*, substitution of one immunosuppressive agent for another) or as a prognostic variable.[18,45]

Using the parameters outlined in Tables 3–7 as well as "suggestive" clinical features we have established various etiologic diagnoses. However, in 30% of patients, even in retrospect no definite etiology can be established. Similar reservations must be made with respect to many papers on this subject.[1,4,7,8,14,18,24,30,32] We can say that clinical hepatitis due to hepatitis B is uncommon as compared to the number of carriers in the population but when clinical jaundice due to HB$_s$Ag appears it is usually unremitting and fatal.[23,31–34,42,43] Nevertheless, our evidence does not support the idea that dialysis patients positive for HB$_s$Ag should categorically be denied transplant.

This posttransplant incidence of CMV infection is between 75–90%.[2,3,5,11,16,19,38,39,46] The spectrum of liver dysfunction with CMV infection ranges from mild hepatocellular dysfunction to liver failure and death.[1–3,21,24,45] As in the case of HB$_s$Ag hepatitis, we do not know the incidence of hepatic involvement in all our patients with documented CMV infection because of the lack of a prospective study of hepatic function. Three causes of jaundice offer fewer diagnostic problems. 1) *HVH* is a rare cause of severe hepatitis appearing in newborn infants and young children with disseminated infection[15,27] and occasionally in transplant recipients.[20,22,29,40] Jaundice accompanies mucocutaneous vesicular eruptions and the diagnosis can be established by detection of inclusion bodies from mucosal lesions or liver biopsy. 2) *Varicella zoster* hepatitis is even more rare but effective treatment for herpes zoster infection has now been established in the use of arabinoside A. Zoster immune plasma has been established as useful prophylaxis after herpes zoster exposure but its usefulness in treatment is doubtful.[6] 3) Hepatic failure due to systemic bacterial and fungal *sepsis* has long been recognized although the mechanisms involved are poorly understood.[13,18,44] It carries an ominous prognosis.[13,18,44]

The cause for hepatitis in a substantial group of patients is not readily apparent, and in fact the illness is probably associated with multiple causes. Among the common etiologic factors suggested are unidentified viral agents[10,14,45] and drug toxicity with azathioprine receiving prime consideration. Whereas early work by Starzl et al. showed that azathioprine in high doses (2–4 mg/kg/day) can cause hepatocellular necrosis in dogs,[41] other workers[34] suggest that there is no conclusive evidence that azathioprine is an important hepatotoxic agent in man. Since azathioprine can be stopped with relative safety[7,18,45] it would appear that cessation of azathioprine with or without the substitution of cyclophosphamide should be recommended. Other drugs with known hepatotoxic effects are α-methyl dopa, isoniozide,[25] acetaminophin,[28] sulfisoxazole and chlorpromazine. Although we do not feel that the liver failure developing in our patients could be definitively attributed to these drugs, a cessation of these and other known hepatotoxic drugs is in order when dealing with these circumstances.

Ten years ago Moore and Hume[30] discussed the causes of death following transplantation and pointed out that "hepatitis was frequent." Hepatic malfunction appears to be the third leading cause of death following renal transplantation. It is apparent that a number of viruses which cause other syndromes in these transplant patients will, on occasion, be associated with hepatic malfunction, acute hepatitis and more seriously chronic active hepatitis. Very little progress in this area has been made because of a lack of clinical virological correlation for the subclinical illness as well as the severe jaundice. This paper primarily points out the numerous etiologies that can be involved, the difficulty of distinguishing one from the other on clinical ground and the need for precise clinical–virological prospective studies in this susceptible population.

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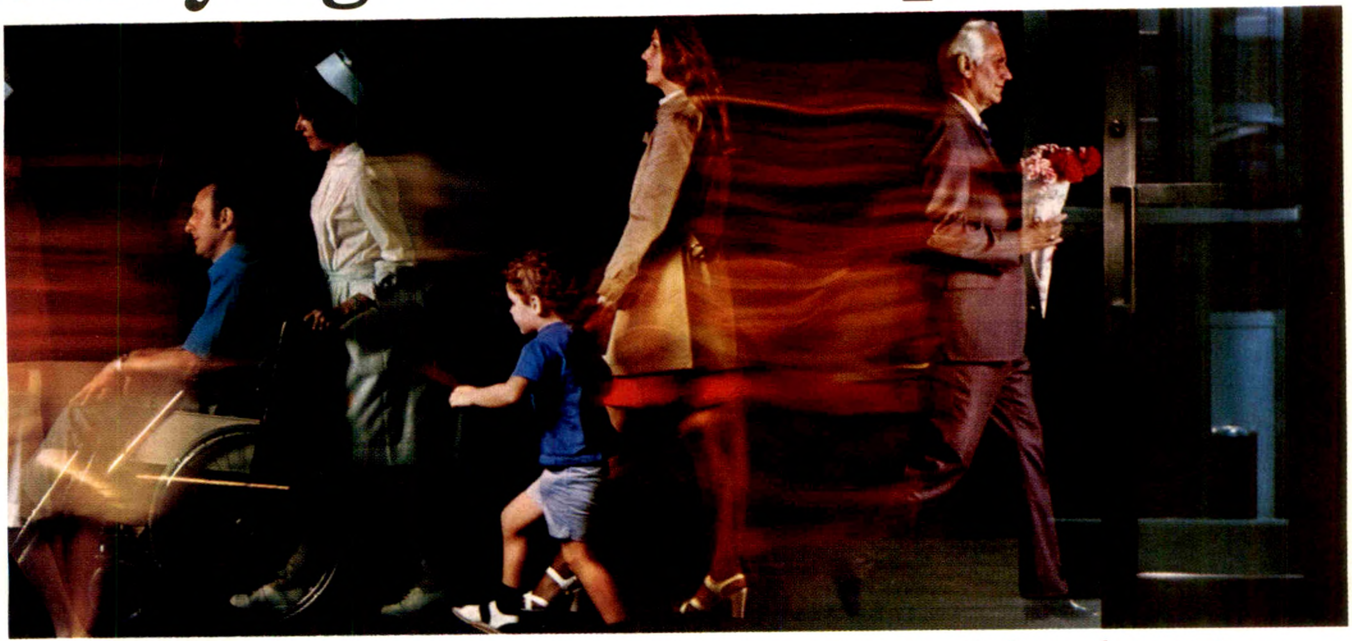
Every day, healthy people leave the hospital—carrying resistant staph.



Today, more than 80%* of community staph is resistant to penicillin G.

Treat these resistant staph infections as effectively in the office as you do in the hospital.

Prostaphlin®
(oxacillin sodium)

*Ross, S. *et al.*: JAMA *229*: 1075 (Aug. 19) 1974.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Prostaphlin® (oxacillin sodium)
Capsule and Oral Solution (11) PROSTAPHLIN 9/11/75

For complete information, consult Official Package Circular.

Indications: Although the principal indication for oxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to oxacillin sodium should be performed.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of oxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to oxacillin sodium, the physician is advised to continue therapy with a drug other than oxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Oxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A previous hypersensitivity reaction to any penicillin is a contraindication.

Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

The possibility of bacterial and/or fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Experience in premature and newborn infants is limited. Caution should be exercised in administration of the drug to such patients and frequent evaluation of organ system function is recommended.

Safety for use in pregnancy has not been established.

Adverse Reactions: The hypersensitivity reactions reported are skin rashes, urticaria, serum sickness and anaphylactic reactions. Oral lesions such as glossitis and stomatitis have been reported. Fever, eosinophilia, oral and rectal moniliasis have also been reported. Hemolytic anemia, transient neutropenia with evidence of granulocytopenia or thrombocytopenia, neuropathy, and nephrotoxicity (oliguria, albuminuria, hematuria, pyuria, and/or cylindruria) are infrequent and usually associated with high doses of parenteral penicillin.

In some newborns and infants receiving high doses of oxacillin sodium (150 to 175 mg./Kg./day), transient hematuria, albuminuria, and azotemia have been encountered. Although the causal relationship is not entirely clear, infants and newborns treated with high doses of the drug should be observed closely for signs of renal impairment.

One patient developed granulocytopenia while receiving intravenous oxacillin sodium and vancomycin. The blood count returned to normal after both drugs were discontinued. Another patient was reported to have leukopenia during intravenous therapy with oxacillin sodium. These counts were made while the patient was moribund. Thrombophlebitis has occurred in a small percentage of patients after intravenous therapy.

Usual Oral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Administer on empty stomach for maximum absorption.

Usual Parenteral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Children weighing 40 Kg. or more should receive the adult dose.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

Supplied: Capsules—250 and 500 mg. in bottles of 48 and 100. Injectable—250 mg., 500 mg., 1 Gm., 2 Gm., and 4 Gm. dry filled vials for IM/IV use. For Oral Solution—100 ml. bottles, 250 mg./5 ml. when reconstituted.

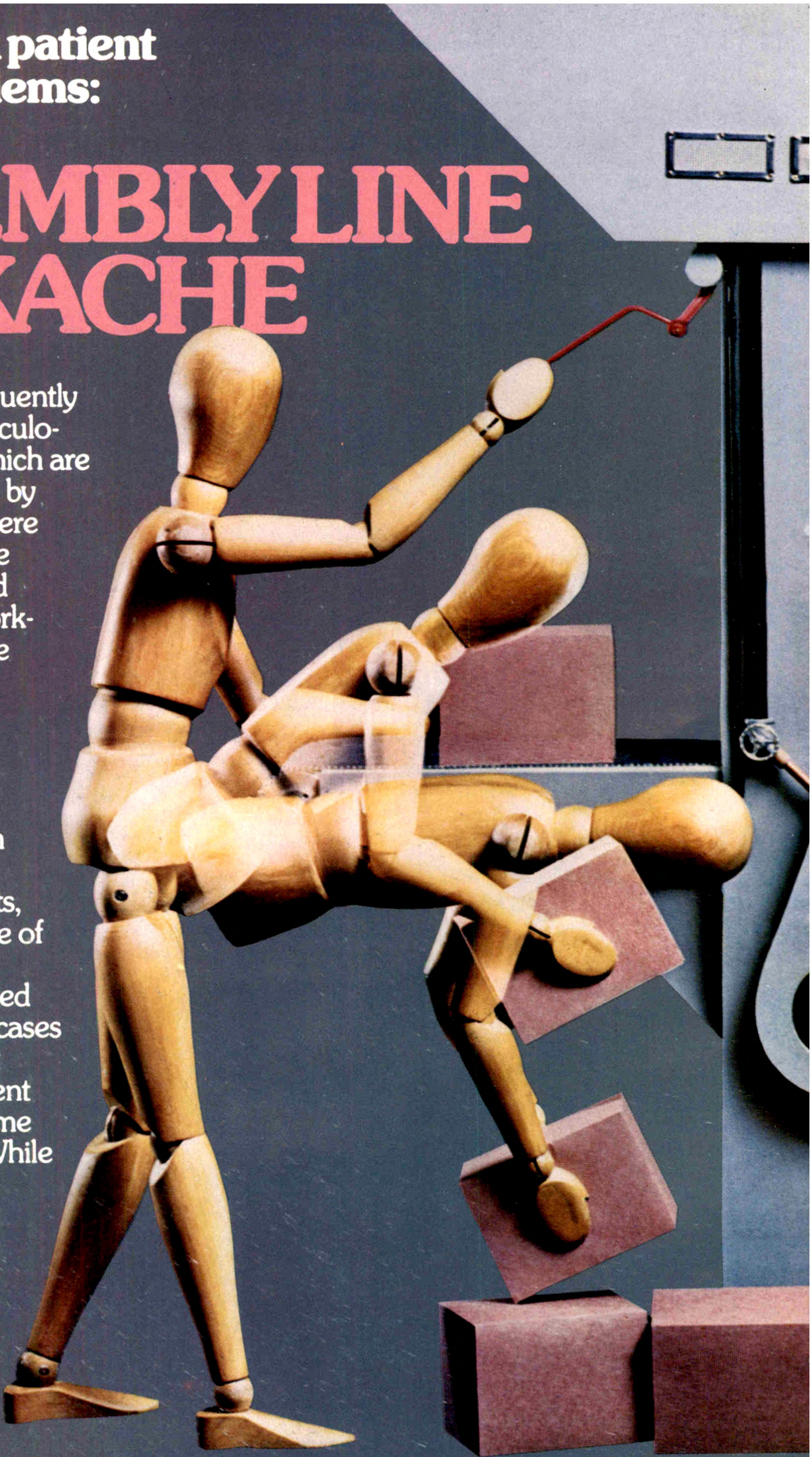
A.H.F.S. Category 8:12.16

BRISTOL®

BRISTOL LABORATORIES
Division of Bristol-Myers Co.
Syracuse, New York 13201

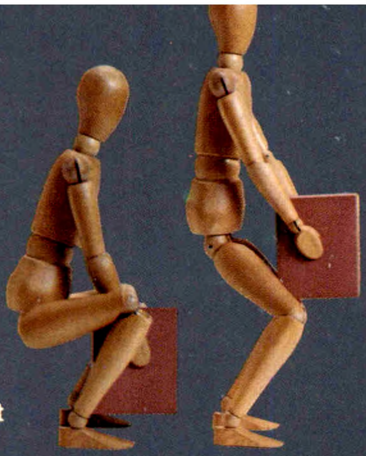
the low-back patient and his problems:

ASSEMBLY LINE BACKACHE



Chances are you frequently see patients with musculoskeletal conditions which are caused or aggravated by assembly line jobs where they must perform the same activity over and over again. Those workers whose jobs require repetitive lifting or bending are most likely to complain of low-back discomfort. Unnatural motions repeated for hours on end can place undue strain on the ligaments, muscles and vertebrae of the lower back, even though the objects lifted are not heavy. These cases are especially difficult to manage if the patient must return to the same job after treatment. While he can't avoid lifting altogether, he can benefit from practical instructions on the correct way to lift and suggestions on how to break up his routine.

Lift with the legs, never the back
This rule applies, even when picking up a scrap of paper. The patient should never bend forward or sideways from the waist, or lift from a bending-forward position. He will better understand why it is important to let the legs do the lifting if you explain that those strong bones and powerful muscles can withstand the strain far better than 24 movable vertebrae in a curved line. You may find it helpful to demonstrate the correct way to lift. Squat in front of the object keeping it close to the body. Then slowly rise to a standing position. The patient should never lift with his legs straight.



Advice to all low-back patients
Avoid lifting objects from car trunks, reaching over furniture to open windows, etc. Don't make beds or run the vacuum cleaner when the back is "acting up." If the patient's job requires repetitive lifting or bending, he should follow correct procedures and periodically take a rest to break up his routine. He may be able to perform the work seated or standing with one foot resting on a small stool. Perhaps his employer can find something different for him to do occasionally. If his back continues to bother him, he will probably have to consider getting a different kind of job.

as an adjunct in the relief of discomforts associated with acute, painful musculoskeletal conditions

ROBAXIN®-750

(Methocarbamol, NF)

750 mg capsule-shaped tablets

the Robaxin regimen:

Bed
Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort.

Board
Have patient insert section of ½" or ¾" plywood between mattress and box springs.

Heat
The judicious use of moist heat is often very beneficial.

Robaxin-750 can relieve the discomforts associated with acute musculoskeletal conditions. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.
It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk. Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.
Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

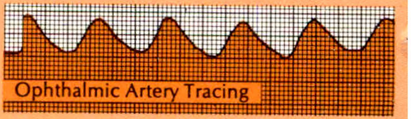
A. H. Robins Company, Richmond, Va. 23220
A-H-ROBINS

The NON-INVASIVE Clinical Vascular Laboratory

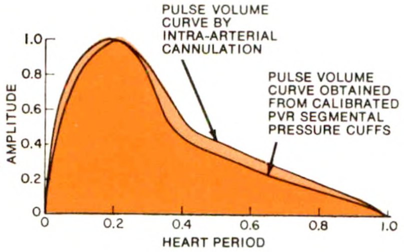
An Extensively Documented Clinical Procedure for the Quantitative Evaluation of Peripheral Vascular Disease:

rterial — Venous — Cerebral

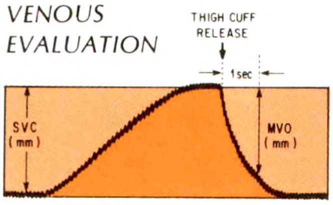
Excellent Long-term Reproducibility and Calibrated Accuracy by Quantitative Segmental Cuff Technique



Ophthalmic artery pressure is read directly on the OPG Attachment of the PVR for the evaluation of collateral circulation to each eye, and its respective cerebral hemisphere.



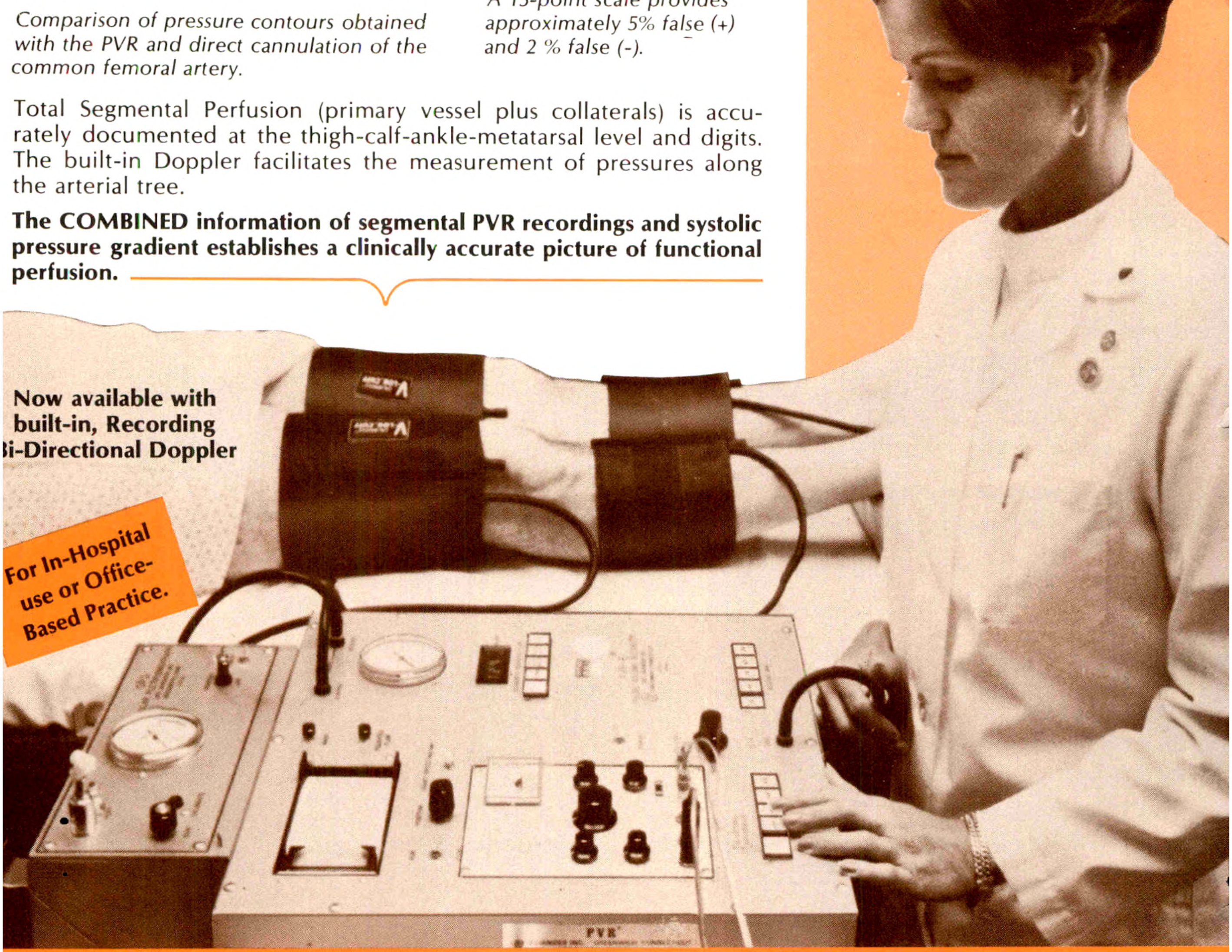
Comparison of pressure contours obtained with the PVR and direct cannulation of the common femoral artery.



A 15-point scale provides approximately 5% false (+) and 2 % false (-).

Total Segmental Perfusion (primary vessel plus collaterals) is accurately documented at the thigh-calf-ankle-metatarsal level and digits. The built-in Doppler facilitates the measurement of pressures along the arterial tree.

The COMBINED information of segmental PVR recordings and systolic pressure gradient establishes a clinically accurate picture of functional perfusion.



Now available with built-in, Recording i-Directional Doppler

For In-Hospital use or Office-Based Practice.

eimbursement for In- and Out-Patients under: Various non-profit hospital and medical-surgical service plans
Medicare • Veterans Benefits • Commercial Insurance Companies.

As Developed by The Vascular Laboratory, Dept. of Surgery, Massachusetts General Hospital, Boston, Mass.

References, bibliography, and details on request.

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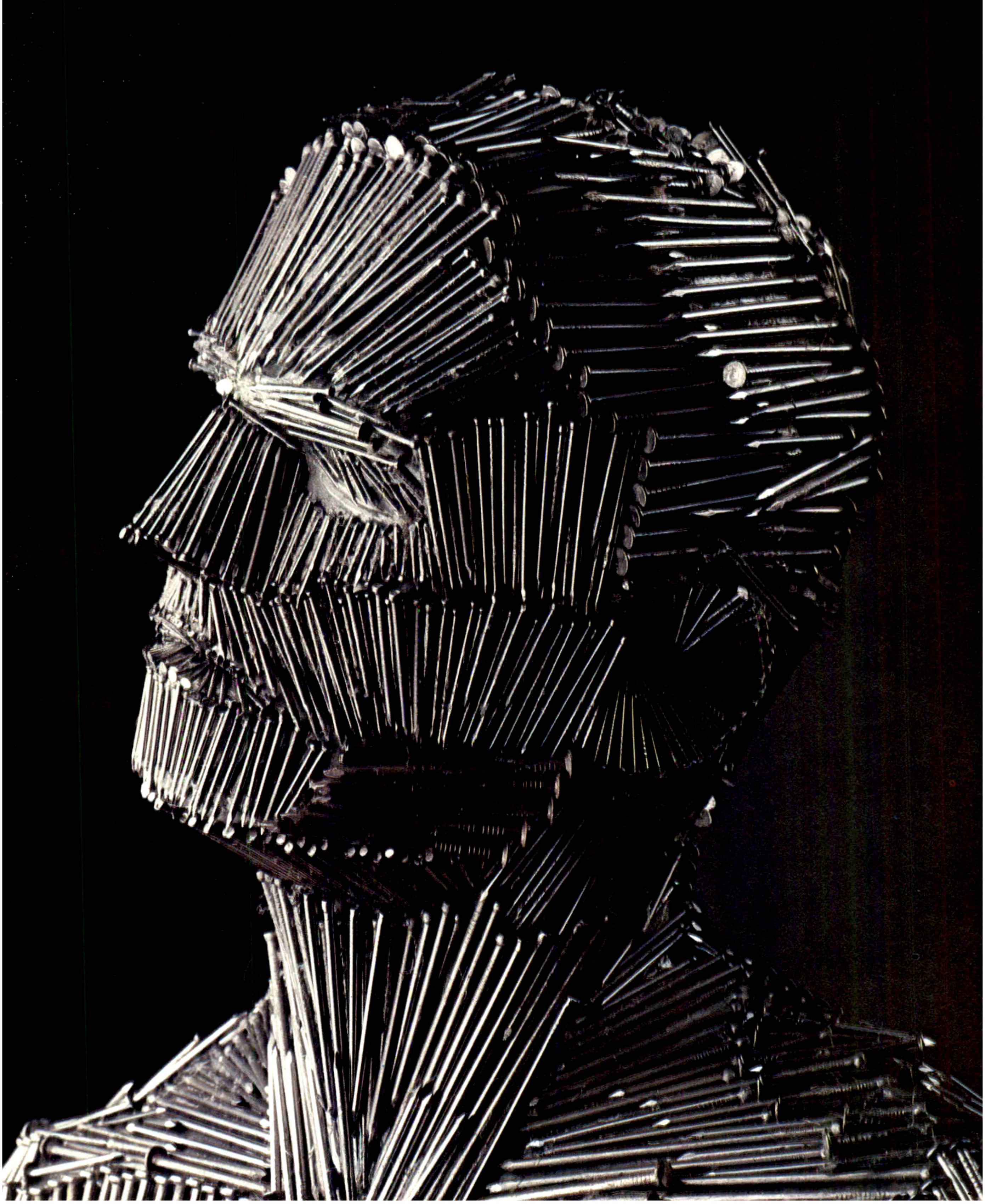
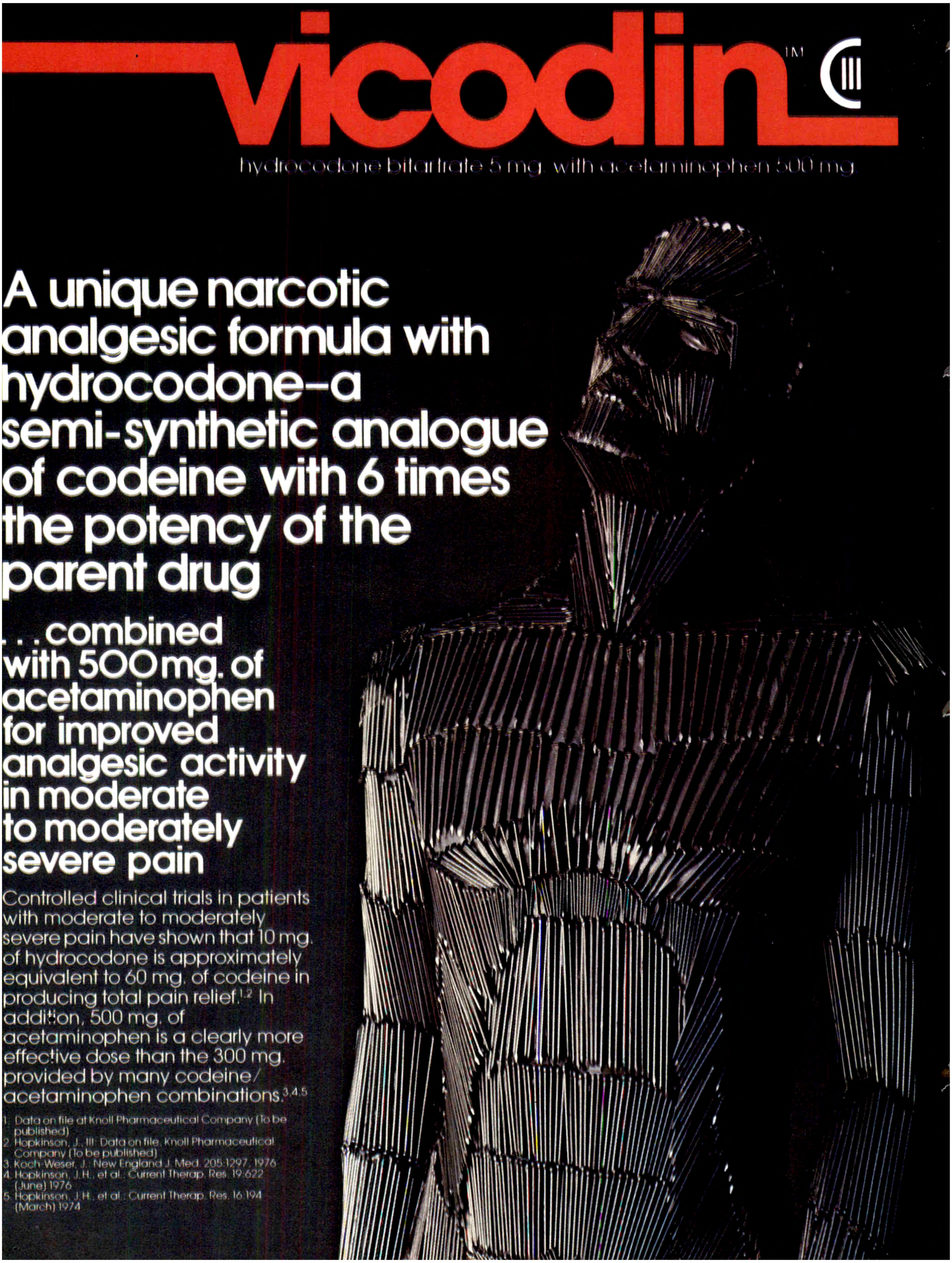
In search of
Victory over pain





vicodin™ CIII

hydrocodone bitartrate 5 mg. with acetaminophen 500 mg

A unique narcotic analgesic formula with hydrocodone–a semi-synthetic analogue of codeine with 6 times the potency of the parent drug

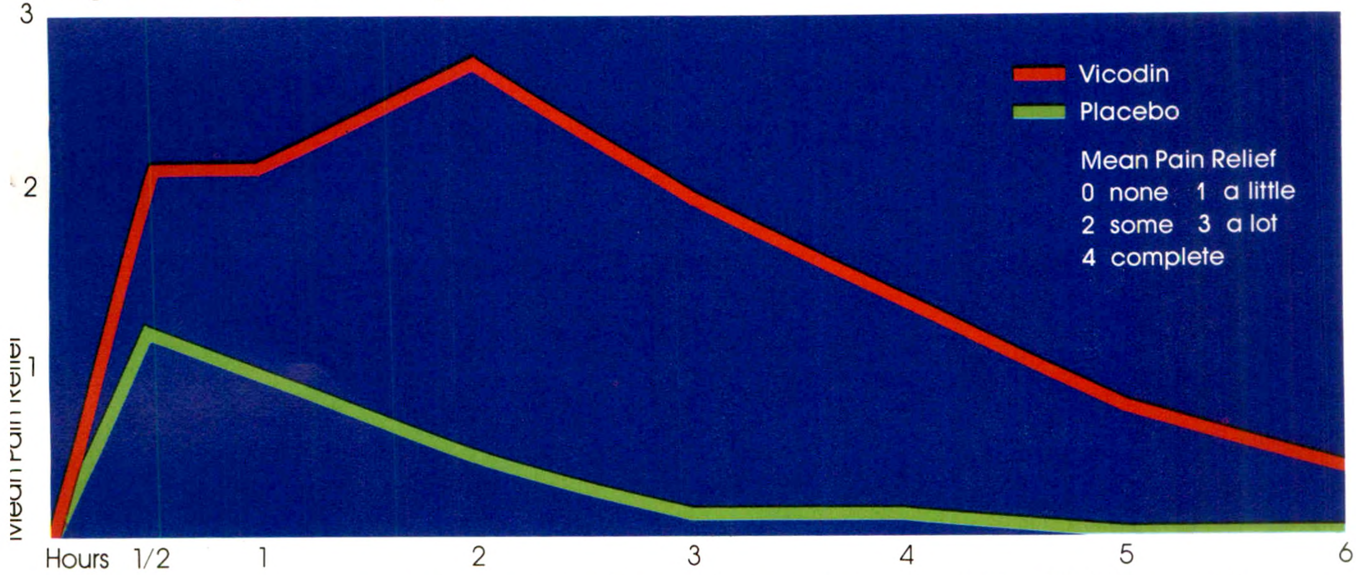
. . .combined with 500 mg. of acetaminophen for improved analgesic activity in moderate to moderately severe pain

Controlled clinical trials in patients with moderate to moderately severe pain have shown that 10 mg. of hydrocodone is approximately equivalent to 60 mg. of codeine in producing total pain relief.[1,2] In addition, 500 mg. of acetaminophen is a clearly more effective dose than the 300 mg. provided by many codeine/acetaminophen combinations.[3,4,5]

1. Data on file at Knoll Pharmaceutical Company (To be published)
2. Hopkinson, J., III: Data on file, Knoll Pharmaceutical Company (To be published)
3. Koch-Weser, J.: New England J. Med. 205:1297, 1976
4. Hopkinson, J.H., et al.: Current Therap. Res. 19:622 (June) 1976
5. Hopkinson, J.H., et al.: Current Therap. Res. 16:194 (March) 1974

A major alternative to combinations of codeine with non-narcotic analgesics

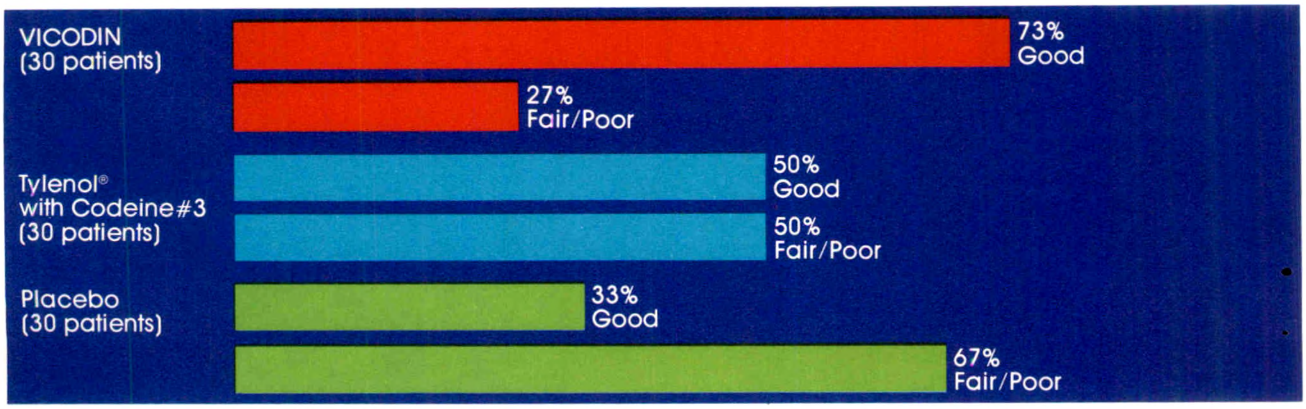
Analgesic effectiveness of VICODIN™ in post operative pain[6]



- In a placebo-controlled double-blind study[6] in patients experiencing moderate or moderately severe pain after surgery, VICODIN was administered to 8 patients and a placebo to 8 others.
- Over a 6-hour evaluation period, VICODIN showed statistically significant superiority in terms of mean pain relief over placebo at hours 2, 3, 4 and 5, after administration.
- In addition, VICODIN was statistically superior to placebo both in terms of total acceptability and total pain relief.

[6] Data on file at Knoll Pharmaceutical Company (To be published)

Analgesic response to VICODIN,™ Tylenol® with Codeine #3, and Placebo in 90 post partum patients[7]



- Three groups of 30 women each with moderate or moderately-severe post partum pain following episiotomy were treated with VICODIN, Tylenol® with Codeine #3, and a placebo.[7]
- In this controlled double-blind study, VICODIN showed statistically significant superiority over Tylenol® with Codeine #3 in terms of overall patient acceptability.

[7] Hopkinson, J. III: Study II, in press.

Tylenol® is a registered trademark of McNeil Laboratories, Inc.

vicodin™ CIII

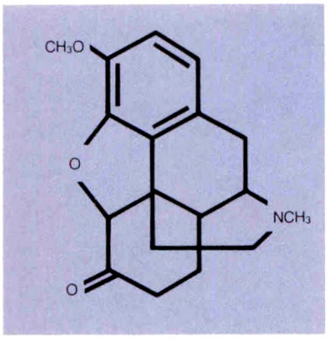
hydrocodone bitartrate 5 mg. with acetaminophen 500 mg.

The convenience of telephone prescribing and Rx refills

VICODIN™ is a schedule III narcotic.

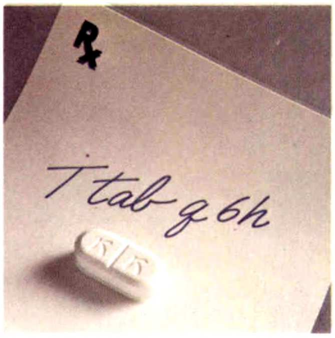
Up to 5 refills in 6 months, at your discretion, where state law permits.

And, prescribing by phone is permissible in most states.



Effective analgesic activity within 30 minutes

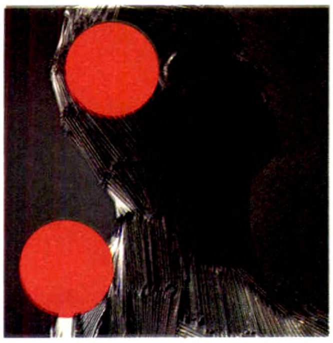
Studies[6,7] show that effective analgesic results can be achieved with VICODIN within 30 minutes.



Long-lasting analgesic effects

The usual adult dose is one tablet every six hours, as needed.

Dosage is adjusted according to the severity of pain and the response of the patient.



Central and peripheral sites of action for greater pain relief

Hydrocodone in VICODIN™ alleviates pain through central effects while the acetaminophen in VICODIN works at the site of pain as well as on the CNS.

Thus, complementary analgesic effects are achieved with two drugs that work at two different sites.

Description: Each tablet of VICODIN contains:
Hydrocodone Bitartrate 5 mg.
(Warning: May be habit forming.)
Acetaminophen (APAP) 500 mg.

Acetaminophen occurs as a white, odorless crystalline powder, possessing a slightly bitter taste.

The hydrocodone component is dihydrocodeinone, a white, odorless crystalline powder which is derived from the opium alkaloid, thebaine.

Actions: The principal analgesic ingredient, hydrocodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; most of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the hydrocodone in this drug are analgesia and sedation.

Hydrocodone is similar to codeine and methadone in that it retains at least one half of its analgesic activity when administered orally.

This drug also contains the non-narcotic antipyretic-analgesic acetaminophen.

Indications: For the relief of moderate to moderately severe pain.

Contraindications: Hypersensitivity to hydrocodone or acetaminophen.

Warnings: Drug Dependence: Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, VICODIN (hydrocodone bitartrate with acetaminophen) is subject to the Federal Controlled Substances Act.

Usage in Ambulatory Patients: Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, VICODIN should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweight the possible hazards.

Usage in Children: VICODIN should not be administered to children.

Precautions: Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of VICODIN or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: VICODIN should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.

Adverse Reactions: The most frequently observed adverse reactions include light headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: The usual adult dose is one tablet every six hours as needed for pain. Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended above in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. VICODIN is given orally.

Drug Interactions: The CNS depressant effects of this drug may be additive with that of other CNS depressants. See **Warnings.**

Management of Overdosage: Signs and Symptoms: Serious overdose with VICODIN (hydrocodone bitartrate with acetaminophen) is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, criculatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of this drug may, in addition, result in acute hepatic toxicity.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Acetaminophen in massive overdosage may cause hepatotoxicity in some patients. Clinical and laboratory evidence of hepatotoxicity may be delayed for up to one week. Close clinical monitoring and serial hepatic enzyme determinations are therefore recommended.

Treatment of acute acetaminophen overdosage is purely symptomatic.

How Supplied: Available as white, bisected, flat capsule-shaped tablets with a double K logo.

- Bottles of 100. NDC #0044-0727-02.
- Hospital Unit – Dose dispenser (reverse numbered 25) available in 100's (4 x 25) pak NDC #0044-0727-01.

PRINTED IN U.S.A. AUGUST 1978

Knoll Pharmaceutical Company, Whippany, New Jersey 07981.
Member Company, Certified Medical Representatives Institute, Inc.

Effects of Protein Depletion and Repletion on Cell-mediated Immunity in Experimental Animals

JOHN M. DALY, M.D., STANLEY J. DUDRICK, M.D. EDWARD M. COPELAND, M.D.

Protein-calorie malnutrition leads to depression of host cell-mediated immunity. Nutritional repletion initially results in rapid weight gain followed by a more gradual return of immunocompetence. Administration of a synthetic amino acid diet to normal animals did not preserve body weight or cell-mediated immunity any better than did a high carbohydrate, protein-free diet. Administration of a synthetic amino acid diet to malnourished animals maintained body weight, but did not restore immunocompetence. Proper nutritional repletion should provide both adequate protein and nonprotein calories if a return of immunocompetence is to be anticipated.

CLINICAL OBSERVATIONS, epidemiologic studies in man, and laboratory investigations in animals have confirmed that protein-calorie malnutrition is associated with depressed immunocompetence and increased susceptibility to infection.[1–19] Several investigators have shown that as many as 30–60 days of enteral nutritional repletion were necessary in children to restore immunocompetence to normal.[6,7] Law Dudrick and Abdou studied malnourished hospitalized adults and found that 18 days of intravenous hyperalimentation (IVH) re-established their patients' immunocompetence.[13] Copeland et al. demonstrated improved immunoreactivity in 13 of 17 anergic cancer patients treated with IVH for an average period of 11 days. These patients were also receiving chemotherapy, and a 50% reduction in tumor mass for a minimum period of 30 days (a positive response to chemotherapy) was demonstrated only in those patients whose immune reactivity improved.[5] Patient investigations are handicapped, however, by the heterogeneity of the patient population and by the inherent difficulty of quantitating precisely the degree of protein and calorie malnutrition. Use of animal models to study immunocompetence allows establishment of controlled nutritional deficiencies in the absence of coexisting illnesses that interfere with accurate interpretation of immunologic data.

From the Department of Surgery, The University of Texas Medical School at Houston, Houston Texas

The purpose of this experiment was to define the time course required in animals for depression and/or restoration of cell-mediated immunity associated with three nutrient regimens: 1) a high carbohydrate, protein-free diet; 2) a carbohydrate-free amino acid diet; and 3) a normal diet. "Protein-sparing" therapy with synthetic amino acids has been advocated as a possible means to preserve lean body mass and immunocompetence.[2] Therefore an additional goal of this experiment was to evaluate whether synthetic amino acids without additional calories as carbohydrate or fat could maintain cell-mediated immunity in well-nourished animals and/or restore impaired immunocompetence to normal in protein-depleted animals.

Materials and Methods

Immunologic Test

Adult Sprague-Dawley rats (Timco) weighing 220–350 g were fed a regular protein diet prior to injecting them in the footpad with 0.1 ml complete Freund's adjuvant (Difco). Ten days later, while still receiving a normal diet, the animals were injected intradermally with 50 μg purified protein derivative (PPD) (Parke, Davis. & Co.) into a shaven flank, and the diameter of induration was assessed 24 and 48 hours later by different investigators. Skin induration greater than 5 mm in diameter was considered a positive delayed cutaneous hypersensitivity response.[14]

Diets

The regular protein diet* (2.97 kcal/g) consisted of 24.5% protein, 4.1% soybean oil and 50% carbohydrate plus all required minerals and vitamins. The formula for the protein-free diet† (4.3 kcal/g) was 85.8% car-

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Presented in part at the Surgical Forum, American College of Surgeons, October, 1976, Chicago, Illinois.

Supported in part by an American College of Surgeons Schering Scholarship (Dr. Daly) CA-16672-02 and McGaw Laboratories.

Submitted for publication: November 26, 1977.

* Wayne Lab-Blox, Allied Mills, Chicago, Illinois.

† Teklad Test Diets, TD 70114, Madison, Wisconsin.

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bohydrate, 8% hydrogenated vegetable oil, 2% cod liver oil, 4% mineral mix (USP XIV, Catalog No. 170880), and all required vitamins. The synthetic amino acid diet, 8.5% FreAmine®, contained all the necessary vitamins and minerals but provided no additional calories as fat or carbohydrate. These three oral diets were fed *ad libitum* throughout their respective study phases. Oral liquid diets facilitated precise measurement of ingested nutrients and included: 1) 25% dextrose—4.25% amino acids (FreAmine®); 2) 30% dextrose; and 3) 8.5% amino acids (FreAmine®). All diets contained the required vitamins and minerals.

Study Phases

A. To assess the reliability of the experimental model for repetitive determinations of the animals' delayed cutaneous hypersensitivity responses to PPD, 20 rats were sensitized with complete Freund's adjuvant and skin-tested with 50 μg PPD (Fig. 1). For the next six weeks, one group of animals (n = 13) was fed a regular protein diet *ad libitum* while the other group (n = 7) was given a high carbohydrate, protein-free diet *ad libitum*. All animals were serially skin-tested with PPD and weighed at two, four and six weeks after initiating their respective diets.

B. To evaluate the effects of protein nutrition on cell-mediated immunity, 20 PPD *positive* animals were fed the high carbohydrate, protein-free diet *ad libitum* and skin-tested with PPD at two, three and five weeks (Fig. 2). By the fifth week, most of the animals were unreactive to PPD. The animals were then paired according to body weight and PPD reactivity. One of each pair of rats was then fed a regular protein diet *ad libitum* while the other of each pair was fed the synthetic 8.5% amino acid diet *ad libitum* without additional fat or carbohydrate calories. Thereafter, body weight and PPD reactivity were measured each week. After three weeks, the group of animals receiving the synthetic amino acid diet was switched to the regular protein diet *ad libitum*. Body weight and PPD reactivity were measured seven and 14 days later.

C. To assess the effects of the oral 8.5% synthetic amino acid diet on immunocompetence in normal well-nourished animals, ten PPD positive rats were fed this dietary regimen *ad libitum* and skin-tested with PPD at two and four weeks (Fig. 3). All of the animals became unreactive to PPD after four weeks. Thereafter, animals were fed the regular protein diet *ad libitum*, and body weight and PPD reactivity were measured every seven days.

D. To evaluate the effects of both protein *and* calorie deprivation on cell-mediated immunity, 14 PPD positive animals were selected randomly to be fed a maximum of 25 ml/day of the 25% dextrose—4.25% amino acid solution orally. This dietary regimen provides young adult rats with approximately one-half of their protein and calorie needs. Additional minerals and vitamins were given to satisfy their complete nutritional

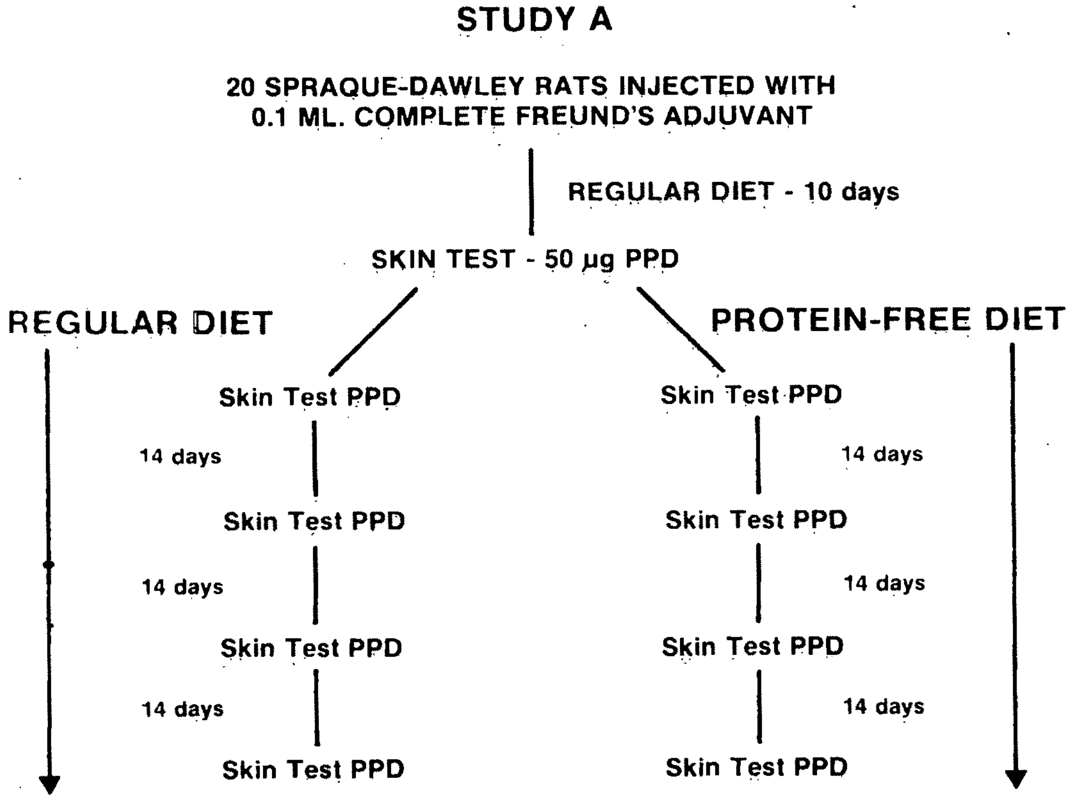

FIG. 1. Study A was designed to assess the reliability of the experimental model for repetitive determinations of the animals' delayed cutaneous hypersensitivity responses to PPD.

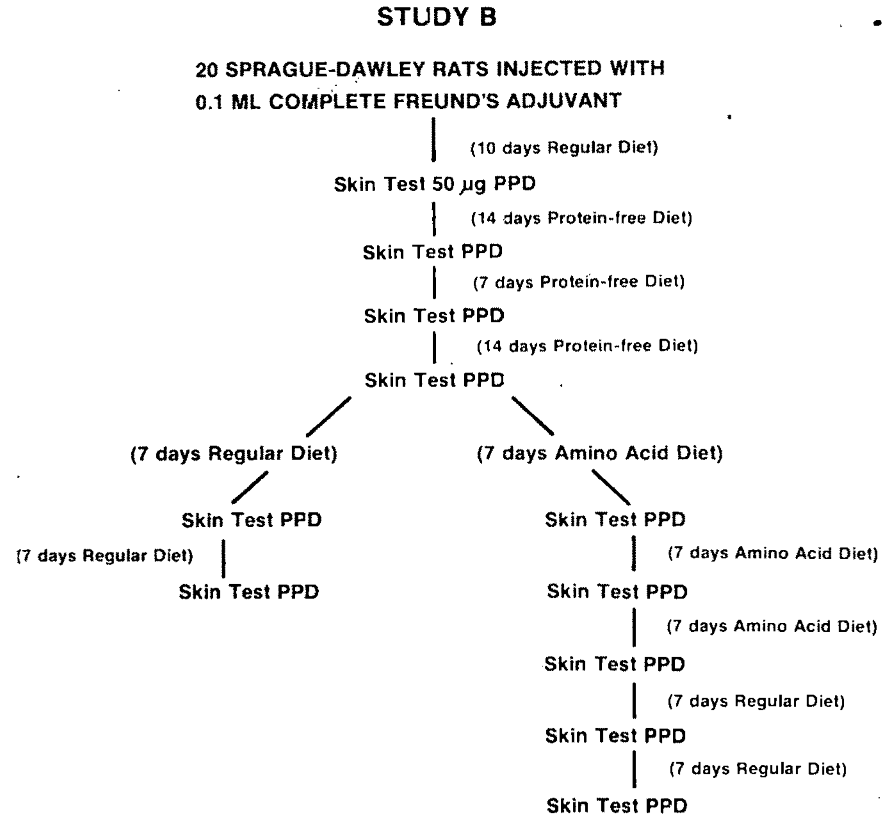

FIG. 2. Study B evaluated the effects of protein depletion and repletion (with and without adequate additional calories) on cell-mediated immunity.

requirements. A second group of 14 PPD positive animals was pair-fed with identical volumes of the 30% dextrose solution orally. This dietary regimen was nearly isocaloric with the dextrose-amino acid solution described and provided approximately one-half of the necessary daily caloric requirement, but none of the protein requirement. Body weight and PPD reactivity were measured in both groups of animals every two weeks for two months. By the eighth week, most of the animals in the 30% dextrose group became unreactive to PPD. These animals were then switched to the 25% dextrose—4.25% amino acid diet (25 ml/animal/day), and body weights and PPD reactivity were measured 7 and 14 days later.

Results

A. After sensitizing 20 rats with complete Freund's adjuvant and maintaining them on a regular protein diet (16 ± 9 g/animal/day—48 kcal/animal/day) for ten days, 13/20 (65%) were PPD positive. The animals were then assigned to diet groups so that 6/13 animals in the regular protein group and 7/7 animals in the protein-free group were PPD positive. As shown in Table 1, 69 to 85% of the rats in the regular protein group were PPD positive at two, four and six weeks. In the protein-free diet group only 14% of the animals were PPD positive at four weeks. At six weeks, by which time the animals had lost an average of 32% body weight, none of these animals reacted positively to PPD.

B. PPD positive animals given the protein-free diet ingested an average of 10 ± 4 g/animal/Day (43 kcal/animal/day) and lost an average of 30% body weight after five weeks (Table 2), and only 4/20 animals (20%) remained PPD positive. The group of ten animals repleted with a regular protein diet rapidly regained their body weight within one week, and after two weeks, 10/10 animals (100%) converted their PPD reactivities to positive.

The second group of ten protein-depleted animals was switched to the oral synthetic 8.5% amino acid diet. These animals maintained their body weights moderately well on the synthetic amino acid diet and lost only an average of 15 g during three weeks. However, only 1/10 of these animals (10%) remained reactive to PPD. When these animals subsequently were switched to the regular protein diet, they all gained weight rapidly, but did not regain PPD reactivity until two weeks.

C. Normal, well-nourished, *PPD positive* animals receiving the oral synthetic 8.5% amino acid diet drank an average of 62 ± 19 ml/animal/day (5.3 g protein/animal/day—21 kcal/animal/day) and lost an average of 33% of their body weight after four weeks (Table 3). At this time, all animals were unreactive to PPD. When switched to the regular protein diet, these animals surpassed their starting body weight in only one week; however, three weeks nourishment with the regular protein diet were required before all animals had regained PPD reactivity.

D. As shown in Table 4, *PPD positive* animals that were both calorie *and* protein restricted (25 ml/animal/day—1.06 g protein/animal/day, 25 kcal/animal/day) lost an average of 12% body weight during eight weeks, but 14/14 animals (100%) remained PPD positive. In contrast, the animals pair-fed the 30% dextrose solution (30 kcal/animal/day) lost an average of 37% body weight during eight weeks and only 2/14 animals (21%) remained PPD positive. When these animals initially fed the 30% dextrose diet were switched to the 25% dextrose—4.25% amino acid diet, they gained an average weight of 15 g during two weeks, and 12/14 animals (86%) regained positive PPD reactivity.

Discussion

Cell-mediated immunity plays an important role in determining the ultimate outcome of organ transplantation, tumor growth and infection such as tuberculosis, candidiasis, herpes simplex and measles.[9–11,15,19] One test for assessing the cell-mediated immune system is the delayed cutaneous hypersensitivity reaction. This reaction has at least three separate components.[6] The sensitization (afferent) limb entails immunization of thymus-derived (T) lymphocytes against a macrophage-processed antigen. The recognition (efferent) limb is characterized by lymphokine production in sen-

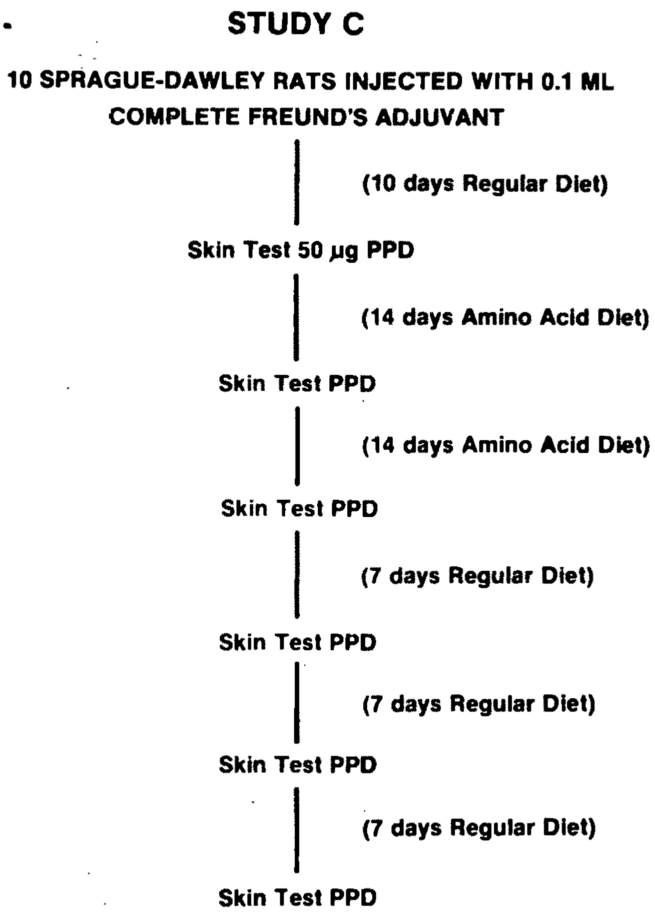

FIG. 3. Study C was designed to measure the effects of an oral amino acid diet (without additional fat or carbohydrate calories) on immunocompetence.

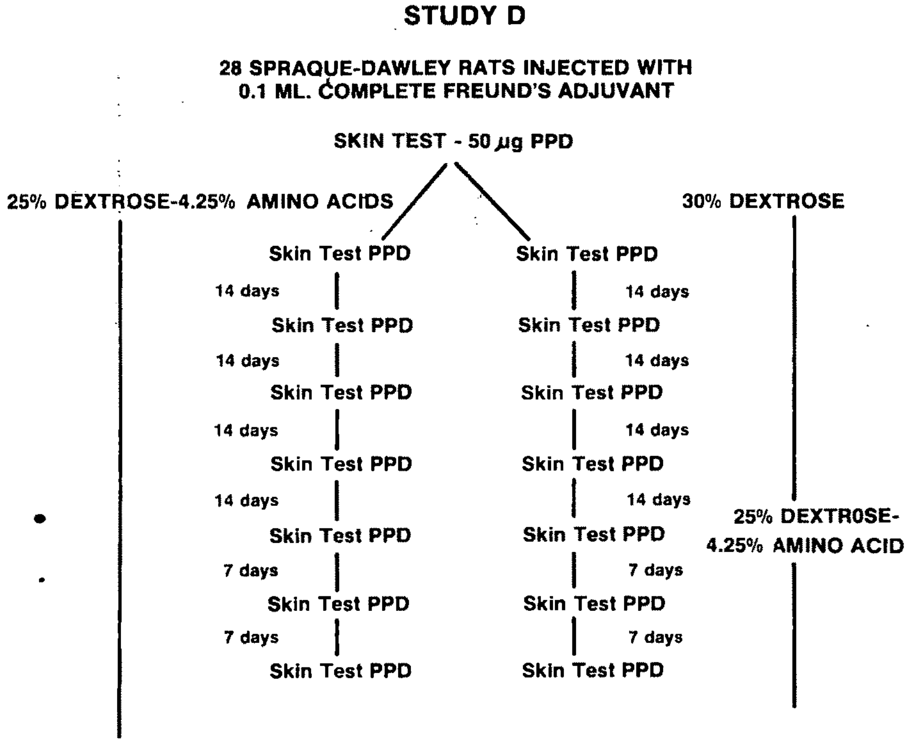

FIG. 4. Study D evaluated the effects of both protein and calorie deprivation on cell-mediated immunity.

sitized (T) lymphocytes after they recognize and interact with the antigen injected into the skin. A significant inflammatory reaction, induced by lymphokines released at the skin site, is read as a positive skin test. A defect in any one of the three components of this reaction may account for an impaired skin-test response. Edelman et al. studied the cell-mediated immune system *in vivo* in children with protein-calorie malnutrition.[6] Using dinitrochorobenzene (DNCB) and *Candida albicans* antigens, they found that 60–80% of these malnourished children had malfunction of both the afferent and efferent limbs of the cell-mediated immunologic response. All components of the delayed cutaneous hypersensitivity reaction were intact in most of their patients after one to two months of enteral nutritional repletion. Gufhuysen et al. studied 21 children with kwashiorkor and also demonstrated improvement in delayed cutaneous hypersensitivity responses after three to four weeks of adequate enteral nutrition.[7] Katz studied PPD negative malnourished children and found that they converted their PPD reactions to positive after treatment with lymphocyte transfer factor from PPD positive donors.[12] He concluded that the afferent limb of the delayed cutaneous hypersensitivity response was impaired while the efferent limb remained unaffected by protein-calorie malnutrition. Law, Dudrick and Abdou demonstrated depressed humoral *and* cell-mediated immunity in young adult rats that were protein depleted after being fed a protein-free diet for six weeks.[14] Protein repletion of the malnourished animals 48 hours *before* antigen sensitization (afferent limb) resulted in significant supranormal responses in all immune parameters tested. Those animals whose repletion started 48 hours *after* sensitization still demonstrated subnormal responses. They concluded that good nutritional status during the induction and/or proliferative phase of the immune response is critical for full expression of immunocompetence.

Our experimental model using complete Freund's adjuvant as the sensitizing antigen followed by PPD intradermal injection seemed to be a reliable index of delayed cutaneous hypersensitivity since 69–85% of the well-nourished animals remained PPD positive over a six week test period. In contrast, during the same test period, there was a direct relationship between the percentage of malnourished rats who lost their PPD reactivity and duration of protein-free feeding. In both well-nourished and protein-depleted animals, repeated dermal injections of PPD antigen did not increase the percentage of rats with positive responses. It should also be noted that in subsequent experimental phases, all animals studied demonstrated competent afferent and efferent limbs of the cell-mediated immune system prior to dietary manipulation.

TABLE 1. *Relationship of Dietary Composition to Immunocompetence*

Weeks on Diet	N = 13			N = 7		
	Diet	Body Weight (g)	% PPD	Diet	Body Weight (g)	% PPD
Start	RD	220 ± 15	46	PF	218 ± 13	100
2	RD	241 ± 13	85	PF	196 ± 16*	29*
4	RD	249 ± 11	69	PF	189 ± 15†	14*
6	RD	259 ± 14	69	PF	168 ± 13†	0*

RD = Regular diet. PF = High carbohydrate, protein-free diet. *$p < 0.05$. †$p < 0.001$.

TABLE 2. *Relationship of Changes in Dietary Composition to Immunocompetence*

Weeks on Diet	N = 10			N = 10		
	Diet	Body Weight (g)	% PPD	Diet	Body Weight (g)	% PPD
Start	PF	347 ± 17	100	PF	347 ± 23	100
2	PF	298 ± 15*	100	PF	283 ± 25	100
3	PF	285 ± 16†	100	PF	272 ± 22	100
5	PF	262 ± 14†	20*	PF	248 ± 28†	20*
1	RD	340 ± 20	10*	AA	252 ± 33†	10*
2	RD	382 ± 29	100	AA	243 ± 35†	20*
3				AA	233 ± 35†	10*
1				RD	283 ± 63	0*
2				RD	355 ± 54	100

AA = Amino acid diet. PF = High carbohydrate, protein-free diet. RD = Regular diet. *$p < 0.05$ Compared with starting value. †$p < 0.001$.

In study *B*, animals repleted with a regular protein diet rapidly regained their initial body weights within one week, but two weeks of nutritional repletion were required *before all* animals regained PPD reactivity. Administration of the synthetic amino acid diet to protein depleted animals maintained body weight but did not improve immunocompetence. However, well-nourished animals given the synthetic amino acid diet in study *C* lost one-third of their body weight and became unreactive to PPD during the four week experimental period. Once again, several weeks of nutritional repletion were required before all animals regained

TABLE 3. *Relationship of Dietary Balance to Immunocompetence*

Weeks on Diet	N = 10		
	Diet	Body Weight (g)	% PPD
Start	AA	269 ± 21	100
2	AA	224 ± 27	100
4	AA	183 ± 28†	0‡
1	RD	294 ± 26	33*
2	RD	355 ± 30†	22*
3	RD	385 ± 37†	100

AA = Amino acid diet. RD = regular diet. *$p < 0.05$. Compared with starting time. †$p < 0.001$. ‡One animal died.

TABLE 4. *Effects of Protein-calorie Malnutrition on Body Weight and Immunocompetence*

	N = 14			N = 14		
Weeks on Diet	Diet	Body Weight (g)	% PPD	Diet	Body Weight (g)	% PPD
Initial	25%D-4.25%AA	227 ± 36	100	30% D	221 ± 22	100
8	25%D-4.25%AA	202 ± 41	100	30% D	139 ± 17†	21*
1	25%D-4.25%AA	204 ± 42	86	25%D-4.25%AA	161 ± 15†	43*
2	25%D-4.25%AA	176 ± 38	86	25%D-4.25%AA	154 ± 16†	86

* $p < 0.05$. Compared with starting value. †$p < 0.001$.

25% D - 4.25% AA
30% D
25 ml/rat/day (one-half daily requirement)

PPD reactivity. Some investigators suggest that protein is the key dietary substrate required for maintenance of adequate cell-mediated immunity.[11] When the diet comprised of amino acids alone was given to normal animals in our study, body weight and immunocompetence were not preserved any better than when the high carbohydrate, protein-free diet was given. Animals given the synthetic amino acid diet in study *C* were malnourished in terms of total calories ingested per day (average = 21 kcal/animal/day), but received adequate protein, while animals given the high carbohydrate, protein-free diet were protein malnourished, but ingested adequate calories (average = 43 kcal/animal/day). While amino acids alone were unable to maintain immunocompetence, amino acids did improve cell-mediated immunity when additional carbohydrate calories were provided in study *D*. Calorie *and* protein restricted animals in study *D* fed the 25% dextrose—4.25% amino acid diet in limited amounts (25 kcal/animal/day) lost 12% of their body weight over eight weeks, but 100% of the animals remained PPD positive. In contrast, the animals given the 30% dextrose solution isocalorically lost significantly greater weight during the same time period, and only 21% of the animals remained PPD positive. These results agree with the findings of Jose and Good who reported that mice fed protein-restricted diets at a level of 5% protein developed adequate cellular cytotoxic immunity measured *in vitro*.[10,11] Animals fed diets containing 3% or less protein failed to develop significant cell-mediated immunity.

It is often hazardous to transfer nutritional and immunological data obtained in animals to man. However, clinical studies have also demonstrated the adverse effects of malnutrition on immunocompetence. Law et al. and Copeland et al. have shown improved immunocompetence in malnourished patients after 11–18 days of intravenous nutritional repletion in patients with either benign or malignant diseases.[5,13] Since depressed host defense mechanisms may lead to infection and further malnutrition, it seems vital to break this vicious cycle. These results lend further support to the proposition that, whenever possible, nutritional repletion either orally or intravenously should be undertaken *prior* to major surgical procedures or other stressful therapeutic endeavors.

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Muscle and Plasma Amino Acids After Injury:

The Role of Inactivity

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This study is part of an investigation of whether injury is associated with a unique amino acid pattern in muscle and plasma using the total hip replacement as a model for injury. The role of inactivity is examined as a factor in producing the changes observed with injury and associated bed rest. Nineteen preoperative patients and 16 normal subjects received a muscle biopsy following an overnight fast. Blood for plasma amino acids was drawn at the time of the biopsy. Seven patients (Group I) were treated with 90 g/day of dextrose for the first four postoperative days following which a second biopsy was performed. Eight normals were placed on four days of strict bed rest. Four (Group II) received a regular diet and four (Group III) received 90 g of dextrose/day I.V. as the sole nutrient. Both Groups I and III showed increases in valine, leucine, and isoleucine in both muscle and plasma on the postoperative biopsy. The postoperative pattern differed from that observed in either group of normal subjects in that significant decreases occurred in muscle glutamine and histidine, plasma alanine, lysine and glycine. Phenylalanine, tyrosine, methionine and threonine were increased in muscle postoperatively while only phenylalanine was increased in either Group II or III of the normal subjects. Plasma phenylalanine increased in the patients while remaining unchanged in normal subjects. The pattern reported here for the patient group differs from that reported for other catabolic states (uremia, starvation, etc.), as well as inactivity with or without partial starvation. This study suggests that injury in the form of a total hip replacement is associated with a unique amino acid pattern of muscle and plasma which differs from that observed in other catabolic states. Bed rest plus partial starvation causes a pattern with certain similarities but cannot account for the postoperative changes observed.

A PROMINENT FEATURE of the postinjury state is increased nitrogen excretion which is felt to reflect mainly the breakdown of muscle protein. This breakdown is in excess of what could be explained on the basis of inactivity and starvation, however both may play a partial role. Practically every condition associated with weight loss and nitrogen wasting is thought to be associated with a translocation of amino acids from muscle to liver. The mechanism and significance of these changes are incompletely understood. The percutaneous muscle biopsy technique of Bergstrom[2] has been used extensively to study changes in muscle composition with various disease states and exercise. Studies[1,3,4,14,18] have indicated that the intracellular amino acid pattern of muscle differs from plasma and that various disease states are associated with their own specific patterns (*i.e.* uremia, starvation, lactic acidosis) in muscle.

Vinnars et al.[1] have recently suggested that a unique pattern may be associated with injury. The classical work of Deitrick suggests inactivity to be associated with muscle wasting even if nutrition is adequate,[10] while semistarved but active muscle is preserved.[9] Although muscle wasting during severe injury or infection is greater than could be accounted for on the basis of inactivity and starvation both may play a role in the amino acid patterns obtained.

This study compares plasma and muscle amino acid changes of patients undergoing total hip replacement whose sole nutrient was 90 grams of dextrose/day to normal subjects on 1) bed rest plus a regular diet and 2) bed rest plus 90 g of dextrose/day only.

Methods

Nineteen patients (Group I) undergoing total hip replacement were hospitalized on a metabolic research unit for two to three days before and five days after operation. The nature, purpose and possible risks involved in the muscle biopsy technique were explained to the patients and their voluntary written consent obtained. All patients were active and healthy except for

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Supported by NIH Grant #GM 14546 and U.S. Army Contract #DA 49-193MD-2552.

Submitted for publication: March 6, 1978.

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pain and disability associated with bony degeneration of the hip. All patients appeared well nourished, on a regular diet and had normal SMA-6, SMA-12, urinalysis and chest film. Patients with evidence of diabetes, renal or hepatic disease were excluded. On the morning of the operation, each patient had a percutaneous muscle biopsy taken immediately after the induction of anesthesia. Seven patients received 90 g of dextrose/day for the first four postoperative days as the sole nutrient and were biopsied a second time. Eight hours prior to the second biopsy the dextrose infusion was changed to normal saline at a rate of 40 ml/hr. Local anesthesia (xylocaine 1%) was used for the second biopsy and confined to the skin only. Appropriate amounts of water, electrolytes and vitamins were given daily. All patients were on strict bed rest. All biopsies were from the non-operated thigh.

Sixteen normal subjects received a muscle biopsy following an overnight fast. All subjects were aware of the risks of the study and gave signed written consent. Medical history, physical exam and blood chemistries were within normal limits. Eight subjects were maintained on a protocol of strict bed rest for four days following which the muscle biopsy was repeated. Members of Group II (four subjects) were on a regular diet. Members of Group III (four subjects) received 90 g of dextrose I.V. per day as the sole nutrient plus an appropriate quantity of water and electrolytes. The dextrose infusion was changed to normal saline at a rate of 40 ml/hr eight hours prior to the second biopsy.

The muscle biopsies were taken from the lateral portion of the quadriceps femoris muscle, about 15–20 cm above the knee, after local anesthesia of the skin. The wet biopsy material was dissected carefully to remove visible fat and connective tissue. The material was then divided into several portions. Two smaller portions (10–15 mg) were used for determination of water, fat and electrolytes. A larger amount (20–30 mg) was used for measuring free amino acids. The methodology for weighing the samples and for the determination of neutral fat, water, chloride and free amino acids in muscle tissue and plasma has been described in detail[3] and is briefly summarized here:

The muscle samples were weighed on an electrobalance (Cahn RG) for five minutes after biopsy and the wet weight is extrapolated to zero time. Water is determined by weighing before and after drying at 90°. Neutral fat is extracted with petroleum ether. The dried fat free pieces are extracted in 0.25 ml 1 N HNO_3. The wet weight muscle tissue specimen is homogenized. The protein is directly precipitated in 0.5 ml ice cold sulphosalicylic acid. The precipitated sample is stored for 60 minutes at 4° and thereafter centrifuged, decanted and the pH of the supernatant solution is adjusted to 2.2 by addition of 2.5 N LiOH. The neutralized supernatant is freeze dried and reconstituted with Li-citrate buffer and analyzed with an amino acid analyzer modified for use with small samples from one previously described.[11]

The determinations of extra- and intracellular muscle water was based on the chloride method. Chloride is freely diffusible across the skeletal muscle fiber membrane and is distributed according to Nernst's equation. Taking the resting membrane potential of muscle in normal man to be −87.2 mV,[6] the Cl_e/Cl_i ratio is calculated from Nernst's equation to be 26:1. Thus if the total water and chloride content of the muscle tissue and the extracellular concentration of chloride (obtained by correcting the plasma chloride concentration for a Donnan factor and a factor for plasma water[4]) are known, extra- and intracellular water volumes can be calculated.[4]

The intracellular concentration of each amino acid was calculated by subtracting the free extracellular part from the total amount assuming the plasma concentration to be equal to the concentration in the interstitial fluid. The calculation of these relationships has also been described in detail.[3]

TABLE 1. *Muscle Amino Acids Following Total Hip Replacement Versus Inactivity (mMoles/Kg Intracellular H_2O)*

	VAL	LEU	ISOL	PHE	TYR	METH	THR	LYS
Preop	.356	.214	.097	.092	.111	.041	.82	1.15
± SEM	.023	.018	.009	.007	.013	.005	.07	.06
Postop	.682‡	.487‡	.300‡	.201‡	.203‡	.148‡	1.21†	.92
± SEM	.088	.041	.028	.028	.017	.020	.19	.12
Active NL	.350	.283	.134	.077	.106	.050	.85	.773
± SEM	.021	.023	.010	.004	.006	.007	.08	.051
Bedrest	.487*	.358	.153	.114*	.143	.057	.85	.889
± SEM	.074	.050	.033	.016	.037	.012	.08	.156
Bedrest (D_5W)	.540*	.407†	.248‡	.131*	.136	.082	.72	.738
± SEM	.054	.053	.033	.041	.035	.025	.08	.092

* $p < .01$. †$p < .05$, Students t-test. ‡$p < .001$.

TABLE 2. *Muscle Amino Acids Following Total Hip Replacement Versus Inactivity (mMoles/Kg Intracellular H_2O)*

	GLN	ALA	GLY	ARG	HIST	ORN	TAU	ASP	SER	GLU	PRO	AAB
Preop	18.8	2.41	1.68	.72	.324	.345	20.2	2.25	.95	4.06	.76	.145
± SEM	1.17	.14	.11	.06	.019	.032	1.5	.20	.09	.25	.11	.012
Postop	9.50‡	2.34	1.94	.53	.247†	.170†	22.3	1.64	1.00	4.53	.68	.163
± SEM	.71	.29	.15	.08	.024	.026	1.5	.38	.07	.74	.15	.021
Active NL	20.5	2.72	1.56	.603	.390	.417	15.9	2.07	.91	3.13	1.02	.129
± SEM	1.2	.15	.14	.041	.038	.056	2.2	.20	.12	.25	.10	.021
Bedrest	18.6	3.10	1.83	.427	.478	.600	14.7	2.43	1.20	3.17	.237	.129
± SEM	1.4	.33	.37	.108	.059	.070	2.5	.58	.12	.05	.050	.021
Bedrest (D_5W)	14.2†	2.31	1.51	.441	.293	.302	12.5	2.00	1.00	2.72	.630	.243†
± SEM	2.7	.31	.04	.092	.041	.091	1.3	.38	.39	.31	.130	.034

* $p < .01$. †$p < .05$, Students t-test. ‡$p < .0001$.

Results

The postoperative group was compared to the preoperative group using an unpaired t-test. The group of normals on bed rest is compared to the data for active normals using an unpaired t-test. Postoperatively muscle amino acids show significant increases in valine, leucine, isoleucine, phenylalanine, tyrosine, threonine and methionine (Table 1) and significant decreases in glutamine and ornithine (Table 2). Plasma levels of valine, leucine, isoleucine and phenylalanine (Table 3) increase while alanine and lysine decrease (Table 4).

Figure 1 shows the changes in branched chain amino acids in the patient and normal group. The normal subjects on bed rest plus dextrose (Group III) show similar effects to the operative group; however, muscle changes are less marked, while plasma changes are more marked. Figure 2 shows a difference between the postoperative group and the bed rest group. Postoperatively there are increases in muscle phenylalanine, tyrosine and methionine while the normal subjects show either minimal or no changes. Plasma phenylalanine is increased following surgery but not secondary to bed rest alone.

Figure 3 shows the two key gluconeogenic amino acids alanine and glutamine as well as glycine. In contrast to bed rest, the patient group shows a significant decrease in muscle glutamine and plasma alanine and glycine. Figure 4 shows the patients to have a marked decrease in plasma lysine with a small but significant decrease in muscle histidine.

Bed rest alone had minimal effects on muscle or plasma amino acids, the only clear changes being an increase in muscle valine and phenylalanine (Tables 1 and 2) with no significant changes in plasma amino acids. The values for muscle in active normal subjects did not differ significantly from the preoperative group of patients with the exception of an unexplained increased preoperative level of muscle lysine ($p < .001$) and an increased glutamic acid ($p < .02$). Plasma levels of active normal subjects differed from the preoperative patient group in that the patients showed a decreased level of arginine ($p < .02$).

Discussion

Clearly bed rest plus partial starvation for four days can reproduce some changes seen in the postopera-

TABLE 3. *Plasma Amino Acids Following Total Hip Replacement Versus Inactivity (mMoles/Liter)*

	VAL	LEU	ISOL	PHE	TYR	METH	THR	LYS
Preop	.246	.146	.062	.065	.074	.025	.139	.212
± SEM	.014	.008	.003	.003	.004	.001	.008	.009
Postop	.328*	.233‡	.102‡	.089‡	.077	.030	.149	.067*
± SEM	.019	.014	.008	.006	.003	.002	.013	.004
Active NL	.294	.166	.078	.070	.078	.029	.164	.220
± SEM	.020	.012	.006	.005	.005	.002	.010	.014
Bedrest	.297	.198	.089	.089	.091	.037	.168	.258
± SEM	.043	.002	.009	.010	.005	.003	.010	.021
Bedrest (D_5W)	.411*	.300‡	.146‡	.079	.083	.025	.164	.227
± SEM	.022	.014	.014	.004	.002	.003	.020	.025

* $p < .01$. †$p < .05$, Students t-test. ‡$p < .001$.

TABLE 4. *Plasma Amino Acids Following Total Hip Replacement Versus Inactivity (mMoles/Liter)*

	GLN	ALA	GLY	ARG	HIST	ORN	TAU	ASP	SER	GLU	PRO	AAB
Preop	.694	.346	.269	.104	.086	.059	.079	.008	.130	.042	.192	.036
± SEM	.029	.018	.019	.006	.004	.005	.004	.001	.006	.004	.016	.002
Postop	.592	.227*	.192†	.097	.067	.074	.070	.006	.115	.035	.172	.036
± SEM	.035	.019	.014	.009	.004	.008	.005	.001	.008	.004	.018	.004
Active NL	.780	.438	.273	.129	.097	.063	.072	.012	.126	.039	.248	.037
± SEM	.045	.034	.014	.008	.006	.004	.005	.002	.009	.008	.029	.005
Bedrest	.774	.475	.272	.122	.109	.067	.069	.007	.136	.037	.236	.035
± SEM	.020	.032	.025	.012	.004	.009	.005	.002	.007	.008	.043	.006
Bedrest (D_5W)	.690	.308	.235	.114	.091	.053	.080	.005	.130	.017	.174	.069†
± SEM	.040	.027	.031	.012	.008	.008	.008	.001	.012	.003	.036	.006

* $p < .01$. †$p < .05$, Students t-test.

tive group, particularly in the branched chain amino acids. However the aromatic amino acids (phenylalanine, tyrosine) lysine and methionine among the essentials and the nonessential amino acids, glutamine, alanine, glycine, and histidine show changes in plasma and/or muscle following hip replacement which are not seen secondary to bed rest either with adequate nutrition or dextrose alone.

This suggests the changes occurring following injury cannot be explained on the basis of inactivity or nutrition alone. Corticosteroids cause a general increase in plasma levels of many amino acids[5,16,19] and cannot account for the plasma patterns observed in the patient group. Untreated diabetes is associated with an increased plasma leucine, isoleucine and valine with a concomitant reduction in alanine, glycine, threonine and serine.[14] This is similar in some respects to the changes seen postoperatively with the exception of phenylalanine which increases postoperatively, threonine which remains unchanged and glycine which decreases. Insulin may act to decrease mobilization of all, including ketogenic, amino acids and inhibit hepatic uptake of gluconeogenic amino acids,[14] hence a relative insulin deficiency could account for some of the changes observed in the patient group. Starvation alone can cause increases in plasma valine, leucine and isoleucine but does not change plasma levels of tyrosine or phenylalanine and causes de-

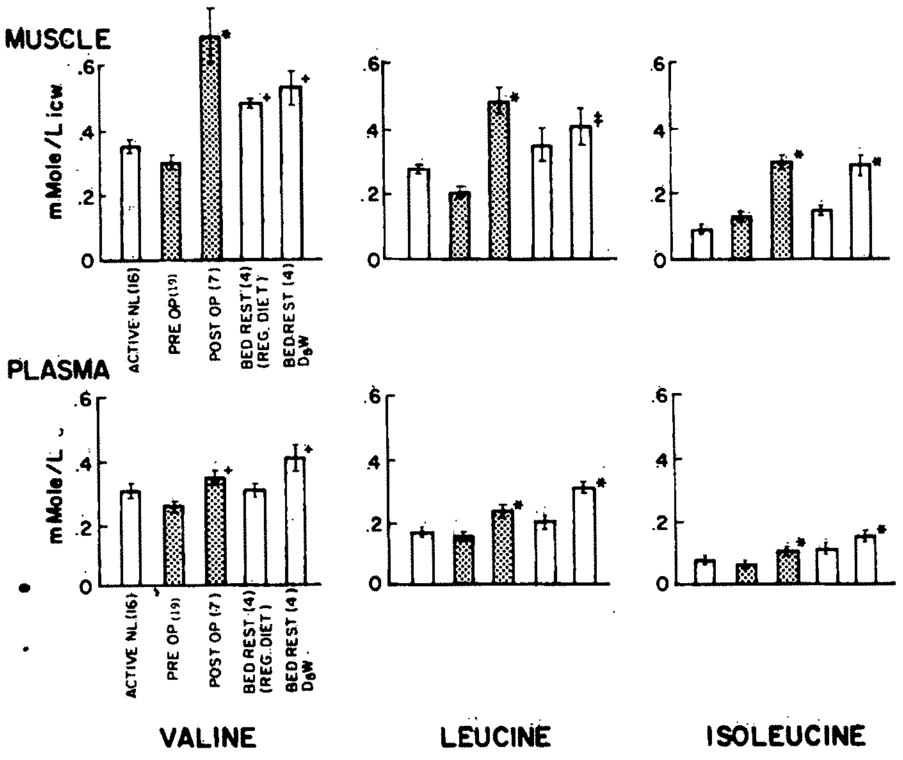

FIG. 1. *$p < .001$. †$p < .01$. ‡$p < .05$.

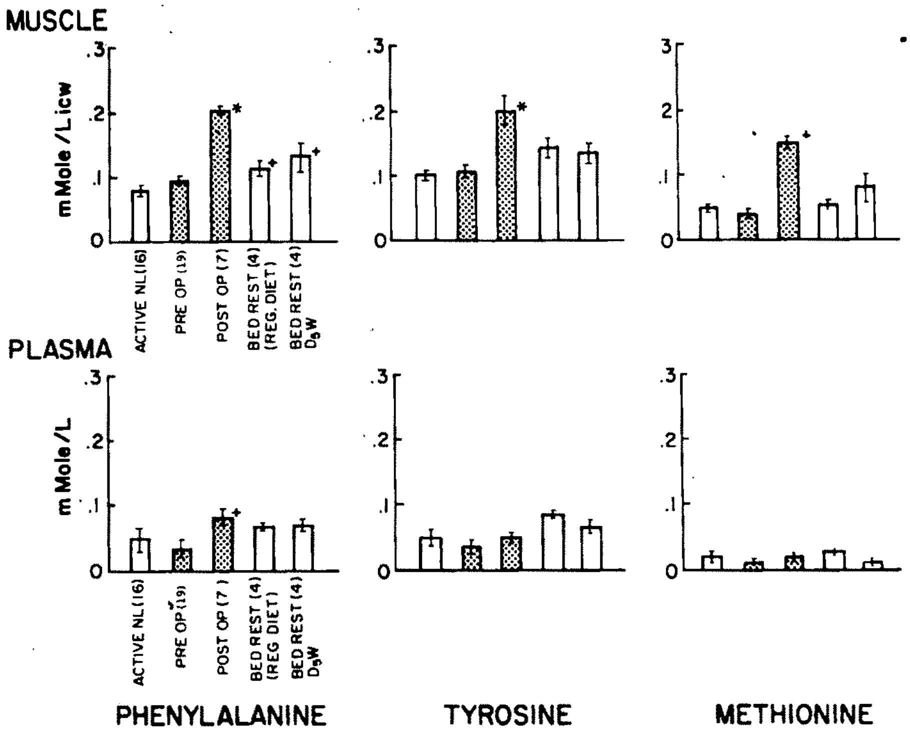

FIG. 2. *p < 0.001. †p < 0.01.

creased levels of alanine.[12] The postoperative group showed a decreased level for plasma alanine while the normal subjects receiving dextrose did not. This suggests that nutrition was not the cause of decreased plasma alanine.

Untreated uremia is associated with low plasma levels of valine, leucine and isoleucine. Muscle valine is decreased in addition.[4] In contrast to uremia, injury and inactivity is associated with increases in the branched chain amino acids which have been sug-

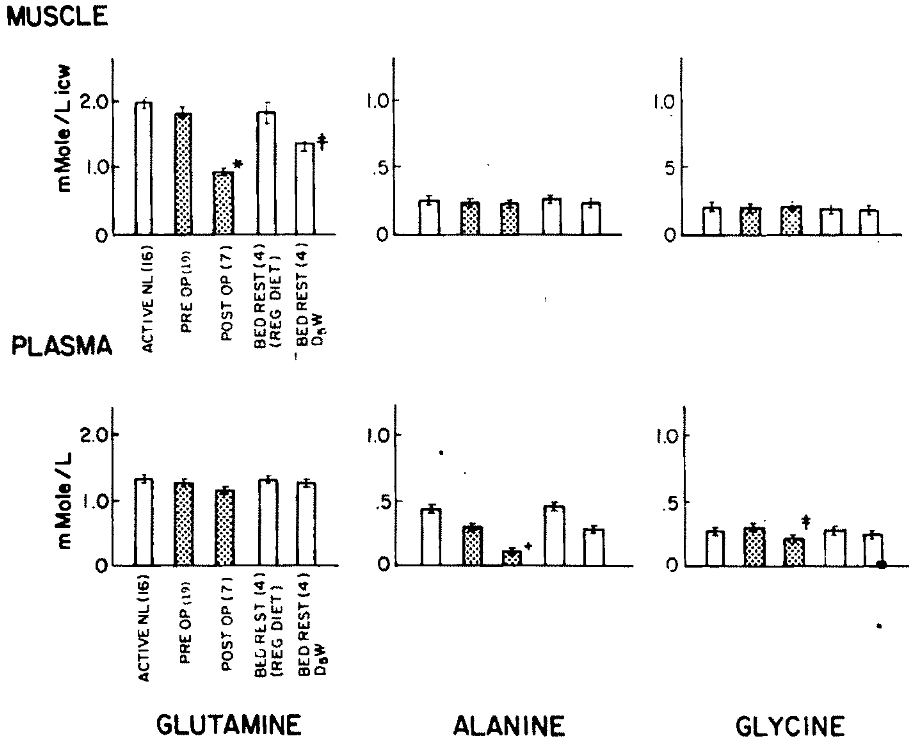

FIG. 3. *p < 0.001. †p < 0.01. ‡p < 0.05.

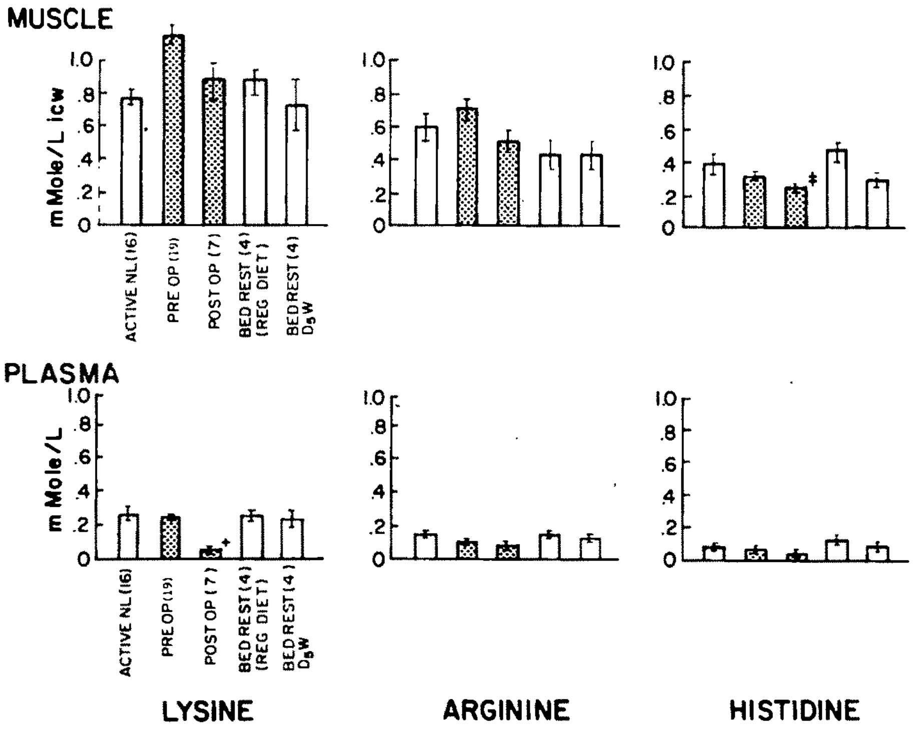

FIG. 4. $\dagger p < 0.05$. $\ddagger p < 0.01$.

gested to be a characteristic of posttraumatic catabolism.[20,21] Inactivity plus starvation in this study was associated with a large decrease in muscle glutamine although less so than the patient group. The depression of essential–nonessential amino acid ratio seen in protein deficiency was not seen in either the patient or normal subjects. This may be due to the fact that this study period was limited to four days and all the subjects were previously well nourished.

Electrolyte deficiency, particularly potassium, can increase levels of lysine, arginine and histidine.[15,16,17] All subjects and patients received adequate amounts of electrolytes and had normal values for serum electrolytes checked on a daily basis. Although there are few reports on amino acid changes in response to inactivity, exercise has been relatively well studied. Brief periods of exercise are associated with increases in alanine levels only.[7,13] With heavier loads isoleucine, leucine, methionine, tyrosine and phenylalanine are increased in plasma.[13]

The pattern reported here in the postoperative group appears to be unique for injury. Clearly some changes can be reproduced by inactivity plus starvation, particularly in the branched chain amino acids. Although certain catabolic states have similarities there are distinct differences following injury from that secondary to starvation, uremia and untreated diabetes.

Summary

The amino acid pattern following total hip replacement is characterized by increases in muscle of the branched chain amino acids (leucine, isoleucine and valine), the aromatics (phenylalanine and tyrosine) as well as methionine. The nonessential amino acids in muscle tend to decline, glutamine having the most marked change. Plasma levels of the essential amino acids increase while the nonessentials tend to decrease. This pattern differs from that observed in other catabolic states (uremia, starvation, untreated diabetes) and is significantly different from the effects of inactivity and starvation combined. This suggests that injury can be characterized by a unique pattern of muscle and plasma amino acids.

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Gastroesophageal Reflux in Duodenal Ulcer Patients Before and After Vagotomy

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Gastroesophageal reflux was investigated in 80 patients with duodenal ulcer by analysis of symptomatology and the acid reflux test. Resting gastroesophageal sphincter pressure (GESP) and postvagotomy reduction in basal and pentagastrin stimulated gastric acid secretion were also studied. Reflux symptoms were present in 40% of the patients, and this incidence was significantly reduced two months after vagotomy. In patients studied late after operation reflux symptoms were still less frequent than before operation, but not significant. After vagotomy, no significant changes in the fasting GESP or in gastroesophageal reflux as determined by the pH glass electrode were demonstrated. Thus, the decrease in reflux symptoms may be explained by the significant reduction in gastric acid secretion. Denervation of the cardia and the lower esophagus does not influence GESP or gastroesophageal reflux.

THE USE OF PARIETAL CELL VAGOTOMY (PCV) or selective gastric vagotomy and drainage (SGV + D) as a definitive treatment for duodenal ulcer (DU) is now well established.[2] During the performance of these procedures, the lower 5–7 cm of the esophagus and the esophagogastric junction are completely isolated. Therefore an extensive denervation of the gastroesophageal segment is achieved and all the surrounding tissues, possibly having an effect on the lower esophageal sphincter, are disrupted.[9]

This study concerns the effect of vagotomy and disruption of the periesophageal tissues on the incidence of gastroesophageal reflux in DU-patients before and after vagotomy.

Materials and Methods

Patients Studied

A total of 80 patients were included in the present study. They were selected randomnly from the follow-up clinic and all gave their consent to take part in this particular investigation. Two main groups were studied:

1) Thirty-two DU-patients with a mean age of 50 years (range 27–73). The ulcer was always verified by endoscopy. Twenty-seven were submitted to randomized surgery, 15 receiving PCV and 12 SGV + D. They were evaluated clinically one month before and two months after surgery. Among these patients, 15 were studied both before and after vagotomy by the pH acid reflux test, besides the analysis of the clinical symptoms. This group is called the "early group."

2) In addition three other groups were studied in the late postoperative period to determine the incidence of reflux in a larger postoperative population. They are considered as the "late group" and consist of the following subgroups:

a) Eighteen patients 32 months after PCV (range 12–54) with a mean age of 55 years (range 27–74).

b) Eighteen patients 28 months after SGV + D (range 8–52) with a mean age of 54 years (range 28–72).

c) Twelve patients 29 months after SGV + precise antrectomy (SGV + A) (range 12–48) with a mean age of 51 years (range 34–72). During the surgical procedure the extension of the antrum was determined by the physiological antrum–corpus border with a glass electrode after stimulation with pentagastrin.

In all operated patients a careful isolation of the distal

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Supported by grant No: 512-7468 from the Danish research Council.

Submitted for publication: March 7, 1978.

0003-4932/78/1200/0804 $00.75 © J. B. Lippincott Company

5–7 cm of the esophagus was performed as part of the vagotomy.

Analysis of Symptoms

A careful clinical analysis of symptoms suggesting reflux esophagitis was performed in every patient.[17] Heartburn, defined as ascending retrosternal burning, appearing postprandially, in the recumbent position, or during exercise. It was graded as following: 1+: occasional, 2+: daily, but relieved by medical therapy, 3+ constant and unrelieved. Regurgitation, defined as effortless appearance of gastric content in the mouth, graded as: 1+: occasional, 2+: daily.

Manometric and pH Studies

An assembly of a pH-glass electrode (Radiometer 29, Copenhagen) and three polyethylene catheters was constructed in order to measure simultaneously intraluminal pressures and pH. The internal diameter of the catheters was 1.65 mm and they were connected to external transducers (Elema Siemens 746, Sweden) again connected to a direct writing polygraph (Elema Siemens Mingograph 82, Sweden). The intraluminal pressures were recorded through 1.0 mm diameter side holes located one of them distally and two 5 cm proximally. The tip of the glass electrode was located at the distal hole and the end of the catheters was closed with a metal tip 4 cm distally to the tip of the electrode. The catheters were constantly perfused with distilled water at a rate of 2 ml/min from a heavy duty infusion pump (Braun Unita I, West Germany) with the glass syringes greased. The characteristics of this system can be summarized as 1) no rise in baseline pressure, 2) a pressure rise rate after sudden occlusion of the recording holes of 140 mm Hg/sec.

This assembly was introduced into the stomach through the mouth after slight pharyngeal anesthesia after a fasting period of 8–12 hours. The patients were lying comfortably, and the following measurements were performed.

Gastroesophageal sphincter pressure (GESP). The resting GESP was measured by the rapid pull through technique with a velocity of 1 cm/sec.[8] In every patient the mean pressure recorded by the three catheters was calculated after at least two basal measurements. End expiratory fundic pressure was taken as the zero reference and GESP was determined in resting state and at the end of the test after the instillation of HCl into the stomach.

Gastroesophageal reflux test. The same technique as described by Pope et al.[13] was used. The pH-electrode was calibrated before each examination with a buffer at pH at 4.6. The fasting intragastric pH was measured. The tip of the glass electrode was then positioned 5 cm above the proximal end of the GES and the intraesophageal pH was recorded. The patients were instructed to swallow a bolus of water in order to "wash" the tip of the electrode. Then the patient was asked to perform maneuvers to induce reflux: Valsalva and leg raising for 30 seconds each. If the fasting intragastric pH was above 4 these maneuvers were not performed and acid was immediately instilled into the stomach after the determination of the resting GESP.

In all patients 300 ml 0.1 N HCl was placed into the stomach through the distal hole of the catheter. The tip of the electrode was placed again in the distal esophagus 5 cm above the proximal end of the GES and the intraesophageal pH was measured. After waiting one minute the maneuvers to induce reflux were repeated: Valsalva and leg raising for 30 seconds each. Then, a wide abdominal belt specially constructed for this purpose was placed around the abdomen of the patient and 10 mm Hg of external pressure was applied to the abdomen. The pH in the distal esophagus was measured during 30 seconds in the same way as described before. This maneuver was repeated with 20 and 30 mm Hg of external pressure applied to the abdomen and every time the intraesophageal pH was determined. At the end of the study, when the belt was taken off, a last determination of GESP and intraesophageal was performed in order to detect changes in sphincter pressure which could occur after the instillation of HCl. The total duration of this examination was between 15–20 minutes. Special attention was given to belching and at least one minute was waited before doing any further measurement.

Thus the pH in the distal esophagus was measured 10 times during this study. Gastroesophageal reflux was considered present if the pH in the distal esophagus was less than 4 during or immediately after at least two maneuvers.[4,9,13]

Acid Secretion

Basal acid output (BAO) and peak acid output (PAO) after pentagastrin were determined before and after surgery in every case and the results expressed in mEq/hour. The dose of pentagastrin was 6.0 μg/kg before the operation and 10.0 μg/kg after the vagotomy. Acid concentration was determined by automatic titration in an autoburette Radiometer, Copenhagen).

TABLE 1. *The Incidence of Heartburn and Regurgitation*

	Heartburn	Regurgitation
Early		
DU (32)	14 (44%)	13 (41%)
Postop (27)	4 (15%)	1 (4%)
Late		
PCV (18)	5 (28%)	2 (11%)
SGV + D (18)	5 (28%)	2 (11%)
SGV + A (12)	7 (58%)	3 (25%)

The early group: Examined before surgery were 32 duodenal ulcer patients (DU). This was repeated in 27 patients two months after surgery. The late group comprises patients approximately 30 months after parietal cell vagotomy (PCV), selective gastric vagotomy (SGV) and drainage (D) or antrectomy (A).

Statistical Analysis

The values are given as mean ± SEM. Statistical significance was considered to exist when $p < 0.05$, evaluated by the Mann-Whitney rank sum test and Fischer exact test.

Results

The incidence of symptoms suggesting reflux esophagitis is shown in Table 1. In non-operated DU-patients, heartburn and regurgitation were present in about 40% of the patients. In several, heartburn corresponded to 2+ or 3+ and was usually of long duration. Two months after surgery a significant decrease in the incidence of symptoms was noted in the same patients ($p < 0.05$). Furthermore, when present, symptoms only corresponded to 1+.

Patients with PCV or SGV + D studied late after surgery showed a lower incidence of symptoms compared to the non-operated DU-patients, but this difference was not significant. Symptoms usually corresponded to 1+ or 2+. Patients with SGV + A studied late after surgery showed a higher incidence of heartburn than non-operated DU-patients, but not significant.

TABLE 2. *The Gastroesophageal Sphincter Pressure (GESP) Before and After Instillation of 300 ml 0.1 N HCl Into the Stomach in Fasting Patients*

	GESP (mm Hg) Mean ± SEM		Fasting IG pH Median
	Resting	After HCl	
DU (20)	22.2 ± 1.2	22.1 ± 1.5	2.0
Postop (15)	26.0 ± 1.5	25.5 ± 1.9	2.2
PCV (18)	25.2 ± 1.7	24.4 ± 1.7	2.5
SGV + D (18)	26.2 ± 1.9	26.8 ± 1.6	3.3
SGV + A (12)	33.3 ± 2.3	30.5 ± 2.7	6.3

Given is also the fasting intragastric (IG) pH. The groups are the same as described in Table 1. Numbers in parentheses indicate the number of patients.

Table 2 shows the median of fasting intragastric pH and resting gastroesophageal sphincter pressure (GESP) for all groups. Non-operated patients showed in all cases a fasting pH below 2.0. Two months after surgery two of the 15 patients evaluated (1 PCV and 1 SGV + D) had a fasting pH above 4. Among patients with PCV studied late after surgery, 14 out of 18 had a pH below 4. Patients with SGV + D studied later in the postoperative period, demonstrated in 9 cases (50%) a fasting pH below 4. Finally patients with SGV + A had a fasting pH below 4 in only one out of 12 patients studied. No significant differences in resting GESP were seen in patients before and after surgery.

No significant differences were found in resting GESP between patients with PCV or SGV + D neither than compared nonoperated DU-patients. Similarly no differences were seen in patients after SGV + A compared to any of the other groups.

At the end of the examination GESP was studied after the instillation of acid into the stomach. No significant change in GESP was noted in any of the groups. No correlation was found between the fasting IG pH and resting GESP for any group of patients included in the present investigation.

Table 3 shows the pre- and postoperative results of the acid reflux test and GESP in 15 patients studied before and after vagotomy. Although there is a tendency for the GESP to rise in the postoperative period, this change is not significant ($p > 0.2$). More importantly, it can be seen that there is neither an increase nor a decrease in the number of patients who have reflux demonstrated during the test conditions. Three patients who did not have reflux prior to operation showed a positive test after vagotomy,

TABLE 3. *The Resting Gastroesophageal Pressure (GESP) and Acid Reflux Test (A.R.T.) in 15 Duodenal Ulcer Patients Before and After Vagotomy*

	Before Vagotomy		After Vagotomy	
Patient No.	GESP	A.R.T.	GESP	A.R.T.
1	24.3	−	29.4	−
2	16.0	+	16.5	+
3	12.7	+	14.0	+
4	16.8	+	27.5	+
5	30.0	−	30.0	+
6	22.5	−	34.0	+
7	28.0	−	25.5	+
8	33.0	−	39.0	−
9	22.7	−	25.0	−
10	31.0	−	29.0	−
11	24.0	−	12.0	−
12	33.0	−	34.5	−
13	16.0	−	12.0	−
14	32.0	+	36.0	−
15	23.0	−	26.0	−
Mean ± SEM	24.3 ± 1.7		26.0 ± 2.3	

and one patient with a positive reflux test prior to surgery lost this reflux after the vagotomy. It can also be seen that the changes in sphincter pressure caused by the operation had no relationship to the presence or absence of reflux.

The results of the acid reflux test in all patients determined by the pH glass electrode are shown in Table 4. Before surgery, DU-patients showed reflux in 35% of the patients studied. None of the patients included in the present study had a spontaneous acid reflux to the esophagus. The correlation between the presence of symptoms of reflux esophagitis and a positive acid reflux test was high in all the groups studied. Patients with PCV studied late after surgery showed similar incidence of acid reflux compared to non-operated DU-patients and to the patients studied early after surgery. After SGV + D and SGV + A a higher incidence of reflux was observed, although the difference was not statistically significant. Tables 5 and 6 show in all groups a significant reduction in both basal and peak acid output after surgery ($p < 0.01$).

Discussion

The results of the present study indicate: first, that patients with DU have a high incidence of GE-reflux. Secondly, that vagotomy does not increase this incidence independent whether antrum is innervated, denervated or resected.

The high incidence of reflux esophagitis in non-operated DU-patients has received little attention in the litterature, although there are some reports suggesting an incidence of around 40–60%.[3,7,11,21] These results have been based on clinical, endoscopical or bioptical studies and in some with simultaneous acid reflux test.[3,7] The exact cause of this high incidence is not known. It could be argued that our patients represent a selected universe who are submitted to surgery. However, the previous reports have been performed in patients who were not candidated for surgery. This high incidence of reflux has even been suggested to be responsible for the epigastric distress in DU-patients.[10] The GESP is normal in these cases and is able to respond to increases in abdominal pressure or to food ingestion. It is possible to postulate that acid and pepsin hypersecretion could help in the development of reflux esophagitis because it is well known that the potency and volume of the refluxed material, the esophageal emptying, tissue resistance *etc.* are factors which contribute to the eventual production of reflux symptoms.[9] The evaluation of the presence of reflux has been performed in our patients by the acid reflux test, which is considered as one of the best ways to determine its presence.[4,9,18]

TABLE 4. *The Incidence of Positive Acid Reflux Test and its Correlation with Symptoms Before and After Vagotomy*

	No.	Per Cent	Correlation with Symptoms
DU (20)	7	35	90%
Postop (15)	6	40	100%
PCV (18)	7	39	100%
SGV + D (18)	10	55	100%
SGV + A (18)	7	58	84%

The groups are the same as described in Table 1. Numbers in parentheses indicate the number of patients.

TABLE 5. *The Basal Acid Output (mean mEq/h ± SEM) and the Reduction in Per Cent Before and After Vagotomy*

	Before Surgery	After Surgery	Per Cent Reduction
DU (27)	4.9 ± 1.5	1.5 ± 0.9	69
PCV (18)	4.9 ± 1.7	1.1 ± 0.3	78
SGV + D (18)	3.6 ± 1.6	1.5 ± 0.6	59
SGV + A (12)	5.0 ± 1.5	0.6 ± 0.5	88

The groups are the same as described in Table 1. Numbers in parentheses indicate the number of patients.

In patients after complete vagotomy of any type, a paradoxical effect was observed: an important reduction in the incidence of symptoms suggesting reflux, being persistent late after surgery while on the other hand the incidence of reflux determined by the acid reflux test is similar or even higher after vagotomy. This could be explained in part by the reduction in the acid and peptic activity seen after surgery, suggesting a certain role of these parameters in the development or maintenance of reflux esophagitis.[9]

During the surgical procedure, two main alterations are obtained: a complete denervation of the lower esophageal sphincter and an isolation of the distal esophagus, which represents cutting of all surrounding tissues which could exert some influence on the GESP. However, neither the GESP nor the incidence of reflux were greatly changed after vagotomy, suggesting that extrinsic innervation of the sphincter and all surrounding tissues have a little importance in the regulation of resting sphincteric tone, and presence or absence of GE-reflux.

TABLE 6. *The Peak Acid Output (mean mEq/h ± SEM) and the Reduction in Per Cent Before and After Vagotomy*

	Before Surgery	After Surgery	Per Cent Reduction
DU (27)	39.4 ± 4.5	16.3 ± 4.3	59
PCV (18)	34.7 ± 2.7	15.4 ± 1.5	56
SGV + D (18)	30.0 ± 1.9	12.9 ± 1.5	57
SGV + A (12)	50.0 ± 4.2	5.9 ± 1.7	88

The groups are the same as described in Table 1. Numbers in parentheses indicate the number of patients.

There are only two reports in the literature which have analyzed the incidence of GE-reflux before and after vagotomy.[5,19] In several other clinical reports concerning duodenal ulcer, it is only mentioned that heartburn might be present, and the meaning of this symptom is not pointed out. Besides the preoperative symptoms have not been analyzed. After truncal vagotomy an incidence of 8–31% of heartburn has been reported.[6,12,15,16,20] SGV is followed by heartburn in 16% of the patients[16] and PCV between 11–18%.[1,4] Clarke et al.[5] studied 32 patients before and after truncal vagotomy by radiological analysis of GE-reflux. Nine patients (30%) showed a positive reflux before surgery, this number increasing to 24 cases after vagotomy. Only one patient was regarded clinically significant in symptomatology.

Temple et al.[19] analyzed 20 patients after PCV by radiological studies and found reflux in five (25%). Thus, these results closely resemble ours both concerning the high incidence of GE-reflux and the low paradoxical incidence of symptoms after vagotomy. This fact can explain why in all clinical reports after randomized surgery, where evaluation was based on clinical studies only, GE-reflux was reported with a low incidence.

Based upon our studies, we conclude that vagotomy does not increase significantly the incidence of GE-reflux when compared to preoperative figures. Symptomatology seems to be less frequent probably due in part to the reduction in the acid–peptic activity of the gastric juice. This study also suggests that GESP has no relation to GE-reflux and that all surrounding tissues that could affect GESP in the prevention of reflux do not seem to have any significant role.

Acknowledgments

We are grateful to Dr. Charles E. Pope II for his suggestions and critical review of this manuscript.

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A Sequential, Prospective Analysis of Immunologic Abnormalities and Infection Following Severe Thermal Injury

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A sequential, prospective analysis of humoral and cellular immune function was performed on 20 burn patients with injuries involving ≥45% total body surface area. Infected patients had significantly worse neutrophil bactericidal activity against *Staphylococcus aureus* 502A than did noninfected patients. Chemotaxis of neutrophils correlated poorly with infection although chemotaxis was frequently abnormal. The opsonic index of serum was depressed early after the burn but returned to nearly normal values by the fourth to the fourteenth postburn day. There was no difference between infected and noninfected patients. Serum levels of IgG, properdin and C3, while initially low, remained within the normal range after the ninth postburn day in both groups. Factor B levels rose rapidly during the first three weeks after injury to more than double normal levels in many patients. Suggestive evidence for consumption of opsonic protein occurred with five of 19 episodes of bacteremia. The responsiveness of isolated lymphocytes to PHA was normal. However, patients' sera were shown to significantly inhibit the responsiveness of normal lymphocytes to PHA. Analysis of immunologic profiles for individual patients indicates that abnormalities of neutrophil function are the most important acquired defect predisposing patients to the development of bacteremia following major thermal injury; abnormalities of opsonic action play a secondary but important role.

A MAJOR THERMAL BURN is the most severe form of injury that man can sustain and survive. Infection has always been the leading cause of death following major burn injuries, and multiple lines of both clinical and laboratory evidence have indicated that an increased susceptibility to infection exists over and above that simply associated with loss of the skin barrier. Indeed, virtually every variable of immunologic resistance to infection has been studied and reported to be abnormal following severe thermal injury.[1] However, these studies have examined only isolated variables, and most were performed before the current practice of intensive nutritional therapy was available. This study was designed to examine the spectrum of immunologic resistance to infection to determine which variables are of primary importance.

From the Surgical Immunobiology Laboratory of the Department of Surgery, the Cincinnati Shriners Burns Institute, and the Paul I. Hoxworth Blood Center, University of Cincinnati Medical Center, Cincinnati, Ohio

Methods

Patient Material and Analysis

Twenty consenting patients with burn injuries involving ≥45% total body surface area were studied over a period of 18 months. Thirteen were children treated at the Shriners Burns Institute (SBI) and seven were adults treated at the Cincinnati General Hospital (CGH). The average burn size was 59.5% total with 44% 3° (burn index = 52). The patients were admitted to study up to 21 days following burn (the average was 13 days, half of the patients were admitted within four days). Informed consent was obtained before each patient was entered. Therapy of the patients was not altered by their participation in this study. All patients received routine topical therapy, initially with silver sulfadiazine with alterations as indicated by surface cultures. Systemic antibiotics were administered only on specific indications, primarily bacteremia. The caloric requirements to reflect basal plus anticipated hypermetabolic demands were estimated for each of the patients, depending on the size of the burn, and an attempt was made to provide these calories by continuous nasogastric instillation in patients unable to voluntarily ingest enough to meet their requirements. In most patients (SBI), daily measurements were made of weight and caloric intake. In 14 patients for whom adequate data were available for the calculation, the average maximum weight loss from preburn weight was 12%. In each patient, there was routine monitoring for evidence of infection, and blood cultures were obtained whenever such existed.

Blood was taken for study three times per week for six weeks or until closure of the wound or death of the patient. At each study interval, the following tests

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Supported by USPHS Grants AI-R936-01A1 and 5P01-GM15428-09.
Submitted for publication: April 4, 1978.

0003-4932/78/1200/0809 $00.90 © J. B. Lippincott Company

were done: measurement of the antibacterial function of neutrophils using *S. aureus* and *E. coli*; chemotaxis of neutrophils; serum levels of albumin, C3(B), IgG, properdin and factor B; measurement of the opsonic activity of serum; lymphocyte response to phytohemagglutinin (PHA); and measurement of inhibition of PHA response of normal lymphocytes in the presence of patient serum. Tests of cellular function were performed on the day of collection, and serum related tests were performed in groups. Patient serum was procured within two hours of collection. Half was divided into aliquots and quickly frozen (−90°) and the other half was dialyzed at 4° for 24 hours against normal saline before division and freezing (−90°). A single large pool of normal human serum (PNHS) from ten normal adults was similarly processed at the beginning of the study to serve as standards and controls throughout the study.

Patients were divided into two groups, infected and noninfected, based upon the presence or absence of a positive blood culture during the period of study. For each test, pooled data were then analyzed comparing infected versus noninfected groups. All of the data available were plotted individually for each of the patients, including major clinical events such as surgery or anesthesia, the administration of blood and blood products, weight, temperature, caloric intake, positive blood cultures and systemic antibiotics.

Tests Performed

The antibacterial function of neutrophils was measured by the technique of Alexander and Meakins[3] using *S. aureus* 502A as the test organism. Results were recorded as a neutrophil bactericidal index (NBI). The NBI is a function of the number of surviving bacteria after the incubation period:

$$\frac{\text{number surviving in patient's test}}{\text{average number surviving in control tests}}$$

Hence, higher numbers reflect poorer phagocyte bactericidal activity. Duplicate tests were performed using *E. coli* 075 as the test organism. Chemotaxis of neutrophils *in vitro* was studied only in the first 12 patients utilizing complement-derived chemotaxins as previously described.[15]

Radial immunodiffusion[17] was used to measure levels of C3(B), IgG, properdin and factor B using nondialyzed frozen sera. All measurements were compared to the control pooled normal human serum (PNHS). Concentrations of C3(B), properdin and factor B in the control PNHS were determined by comparison with standard sera.* Antisera to IgG, C3(β1c/β1a), and factor B were obtained commercially from Behring Diagnostics, Somerville, N.J. 08876. Antisera to C3(B) (the B antigenic determinant of C3) were prepared from anti-β1c/β1a by the method of Molenaar.[18] Properdin was prepared by the method of Ogle et al.,[21] and antisera to properdin were prepared in goats. Albumin levels were determined routinely as part of an SMA-12 group of tests.

The ability of patient sera to support opsonization was performed by a modification of the method of Hirsch and Strauss[12] using 4% concentration of patient serum which was previously dialyzed to remove any antibiotics potentially present. Control PNHS was similarly dialyzed and treated. *E. coli* 075 was used as the test organism. We have found that this strain has a requirement for factor B and properdin for opsonization, but that opsonization proceeds normally in IgG-depleted serum. The ability to opsonize organisms obtained from positive blood cultures was similarly studied using the patient's sera obtained before, after, and nearest the time of the event. The results were expressed as an opsonic index which is:

$$\frac{\log_{10} \text{kill with patient serum}}{\log_{10} \text{kill with control serum}}$$

The response of lymphocytes in whole blood to PHA was determined by the method of Eskola et al.[8] For studying the effects of patient sera on PHA responses with normal lymphocytes, lymphocytes were purified by centrifugation on a Ficoll-hypaque density gradient, washed with Eagle's minimum essential medium (MEM), resuspended in MEM containing penicillin, streptomycin and 5% PNHS (or patient serum) and dispensed (200 μl) into sterile microculture plates (Falcon, Oxnard, California). PHA (0.5 μg) was added to each well. After 48 hours of incubation at 37° in 5% CO_2, 1 mCi of ^{3}H-thymidine (20 mCi/nmole, New England Nuclear, Boston, Massachusetts) was added to each well. After an additional 18–24 hours incubation, the lymphocytes were harvested on glass fiber filters using a MASH III (Microbiological Associates, Bethesda, Maryland) and the incorporation of ^{3}H-thymidine into DNA determined by liquid scintillation spectroscopy. All determinations were performed in sets of six for each patient and included nonstimulated controls.

Normal Controls

Identical tests were performed on twenty normal individuals to provide a basis for comparison to a normal population.

Statistical Analysis of Data

Data are presented as mean ± standard error of the mean. Levels of significance were determined by standard Student's t-tests.

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* Provided by Dr. Douglas Fearon.

Results

Patient Groupings

Thirteen of the 20 patients, hereafter referred to as infected, had 19 episodes of positive blood cultures at some time during the period of observation. The average burn size for infected patients was 62% total/44% 3^{c} (BI = 53) compared to 54% total/46% 3° (BI = 50) for noninfected.

Tests of Neutrophil Function

Infected patients had significantly worse neutrophil function ($p < 0.01$) against *S. aureus* 502A overall than did noninfected patients (Fig. 1). When all patients were divided into two groups according to burn size, those with burns of 45% 3° or greater had an average NBI of 6.0 ± 0.7 compared to 4.9 ± 0.4 for patients with 44% 3° or less ($p > 0.1$).

The antibacterial function of neutrophils against *S. aureus* correlated poorly with the antibacterial function of the same neutrophils against *E. coli* (Fig. 2), and there was no correlation of function against *E. coli* with the development of infection, either when examined individually or as a group (infected versus noninfected). The NBI (*E. coli*) for the infected group was 3.8 ± 0.6 compared to 2.8 ± 0.7 for the noninfected group (p = not significant).

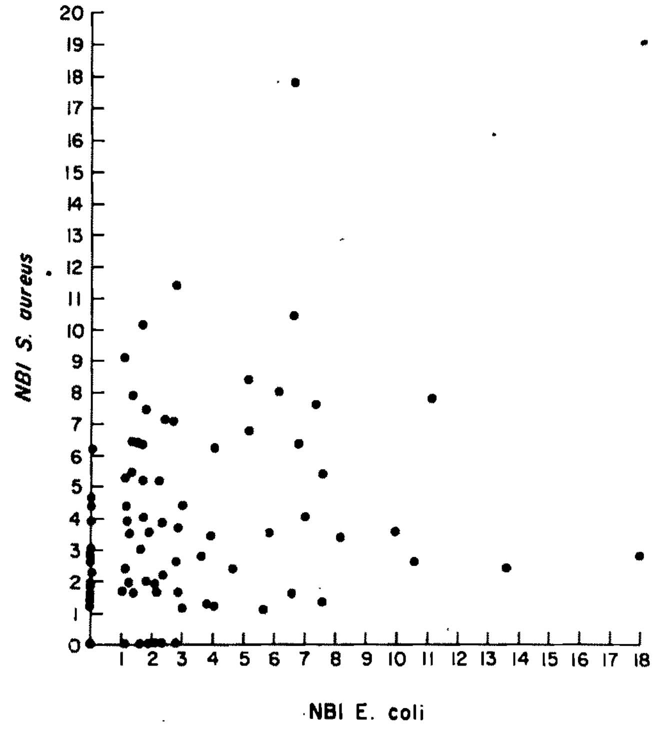

FIG. 2. Scattergram illustrating the lack of correlation between neutrophil function determined using *S. aureus* and *E. coli* as the test organisms. Tests were performed in parallel.

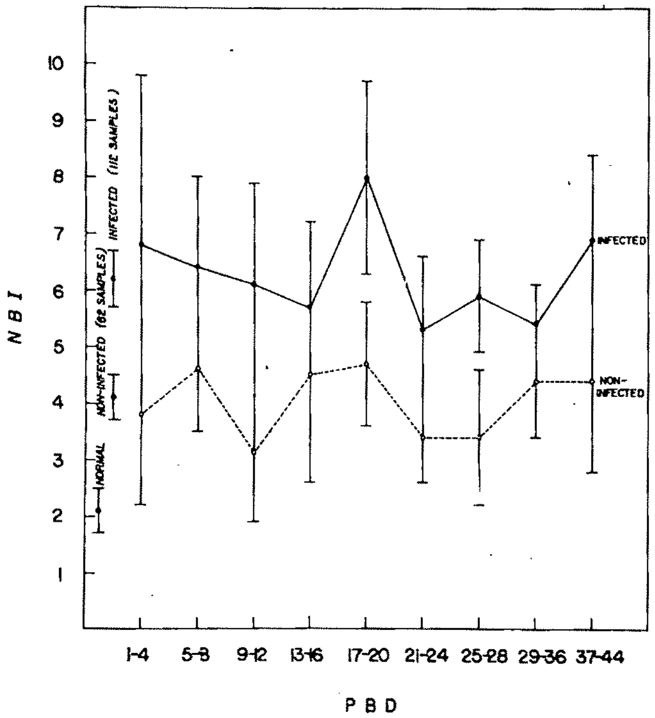

FIG. 1. Sequential neutrophil function (NBI) in burn patients. Values shown are the mean ± S.E.; normal values are 2.1 ± 0.4. The broken line represents patients who were never infected (bacteremic) during the period of study, while the solid line is pooled data from patients who were infected (bacteremic) at any time during the study. Neutrophil function was significantly worse in infected patients ($p < 0.01$).

Chemotaxis of neutrophils also correlated poorly with infection although chemotaxis was frequently abnormal. There was no correlation between the chemotactic index and the NBI using the same samples with tests performed at the same time (Fig. 3). The functional chemotactic index for the infected patients was 100 ± 17, as compared to 76 ± 11 for the noninfected patients. Sequential studies on the same patients showed no relationship to size of burn or ultimate outcome.

Tests of Opsonization

The opsonic index was depressed in all but one patient studied during the first five postburn days, returning to nearly normal values by the fourth to the fourteenth postburn day (Fig. 4). There was no difference between infected and noninfected patients. Similarly, there was no difference in the time-course relationship of the opsonic indices to extent of burn.

Of 13 available organisms isolated from blood cultures, there was no evidence of an organism-specific defect in opsonization in any instance when the infecting organisms were tested comparing PNHS with sequential sera from the infected patient before, during and after the event.

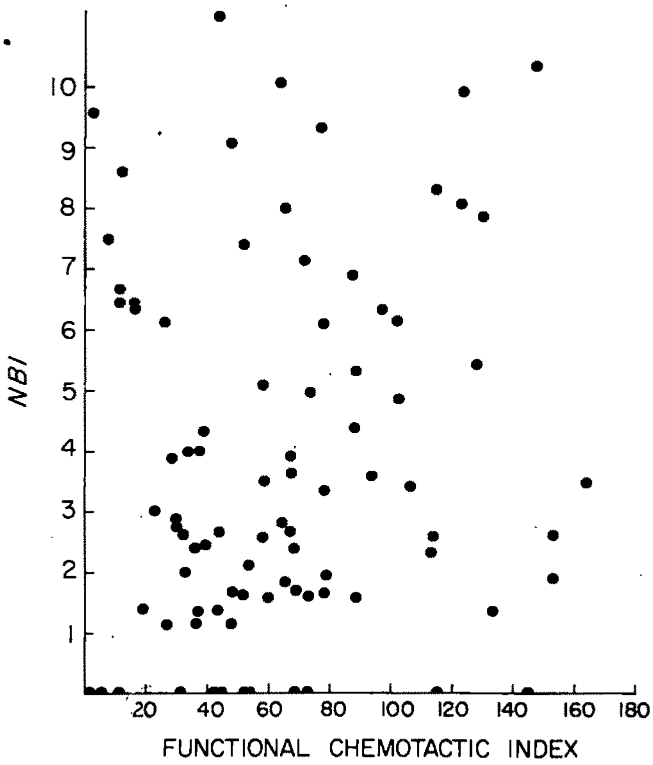

FIG. 3. Scattergram illustrating the lack of correlation between neutrophil function (using *S. aureus*) and functional chemotaxic index (FCI). Tests were performed in parallel.

Serum Concentrations of IgG, Albumin, Factor B, and C3

Serum albumin levels were initially low in both infected and noninfected patients, rising from an average of 2.8 gm/dl on days 1–15 to 3.2 gm/dl by days 36–45 (Fig. 5). However, there was no difference between the infected and noninfected patients.

Serum concentrations of IgG were significantly depressed during the early resuscitative period, rising rapidly between the eighth and twentieth postburn days to high normal levels in noninfected patients and low normal levels in infected patients (Fig. 6). The values for infected patients were significantly lower than for noninfected patients after the thirteenth postburn day ($p < 0.001$), even though they were within normal values.

Properdin levels, while initially low, remained within the normal range after the ninth postburn day (Fig. 7). There were no significant differences between infected and noninfected patients.

Serum concentrations of factor B rose rapidly during the first three weeks after injury to more than double normal levels in many patients (Fig. 8). Infected and noninfected groups were comparable.

C3 concentrations, measured by the B antigenic determinant, rose to higher than normal values during the second week, with only insignificant differences between infected and noninfected groups (Fig. 9). (Data for individual patients are discussed below).

Tests of Lymphocyte Function

The responsiveness of isolated lymphocytes to PHA was measured in only seven patients. In no instances were the lymphocytes abnormal in their ability to be stimulated. However, marked depressions in reactivity were present when responsiveness was measured in the patient's whole blood (stimulation index = 5.3 ± 0.2 compared to normal controls = 22 ± 3). Both dialyzed and nondialyzed serum from the patients inhibited the responsiveness of normal lymphocytes to PHA. There were no differences between infected and noninfected patients (Fig. 10).

Analysis of Sequential Measurements in Infected Patients

Nineteen episodes of bacteremia occurred in the 13 patients in the infected group (Table 1). One patient had three episodes, and two episodes occurred in each

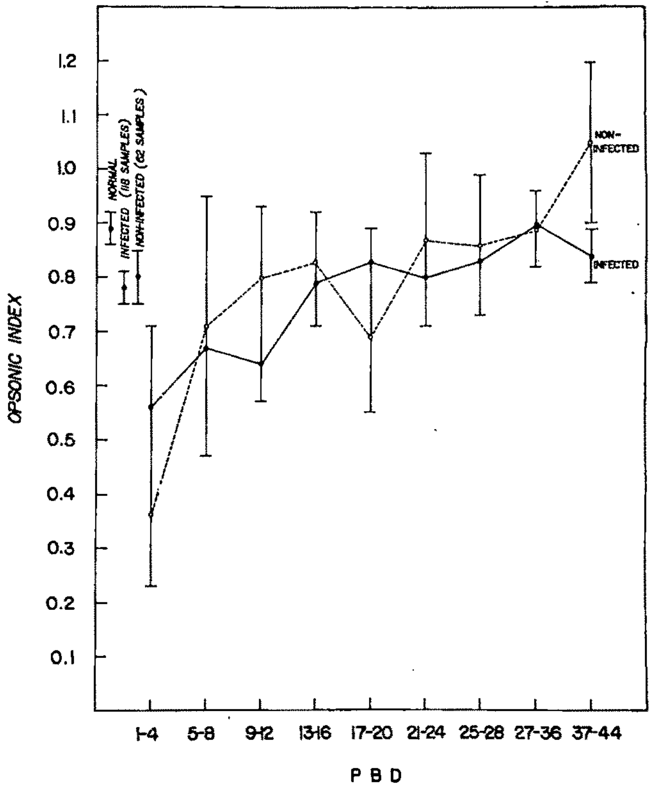

FIG. 4. Sequential analysis of the ability of patient serum to support opsonophagocytosis of *E. coli* 075. Values shown are the mean ± S.E.; normal values are 0189 ± 0.03. A depression in opsonic index is seen the first week following the burn, but returns to low normal by three weeks.

of four patients. Three of the infected patients died, one on PBD 12 from smoke inhalation and pneumonia (59-year-old woman, 63% total/13% 3°), one from a cardiac arrhythmia associated with staphylococcal pericarditis on PBD 28 (12-year-old girl, 55% total/45% 3°, and one from septicemia on PBD 34 (55-year-old man, 80% total/33% 3°). All other patients survived and have been discharged. Eleven of the septic episodes were caused by *S. aureus*, two by *Enterobacter cloacae*, one each by *Klebsiella pneumonia*, *Candida albicans*, *Pseudomonas aeruginosa*, *Streptococcus viridans* and a Bacillus sp. and one episode by multiple organisms: *S. aureus* with *E. cloacae*.

Fourteen of the nineteen episodes of bacteremia were associated with a significant preceding abnormality of neutrophil function against *S. aureus* 502A (NBI ≥ 4) (Table 1). The average NBI immediately preceding all bacteremia episodes was 7.6 ± 1.2. The average NBI was also 7.6 immediately preceding the three infections caused by gram negative bacilli. Two other instances were associated with mild neutrophil dysfunction (NBI 2–4), and neutrophil function was normal (<2) preceding one episode caused by *S. aureus* and one by *P. aeruginosa*. Neutrophil function was not measured before one episode. The NBI improved following eight episodes and worsened following six episodes. Only one episode (4–1) was associated with a preceding normal immunologic profile. This closely followed surgery with extensive mechanical debridement. In seven episodes, the opsonic index was abnormal (greater than two standard deviations from normal) preceding the onset of infection. Neutrophil function was simultaneously abnormal (NBI > 4) at the time of five of these seven episodes.

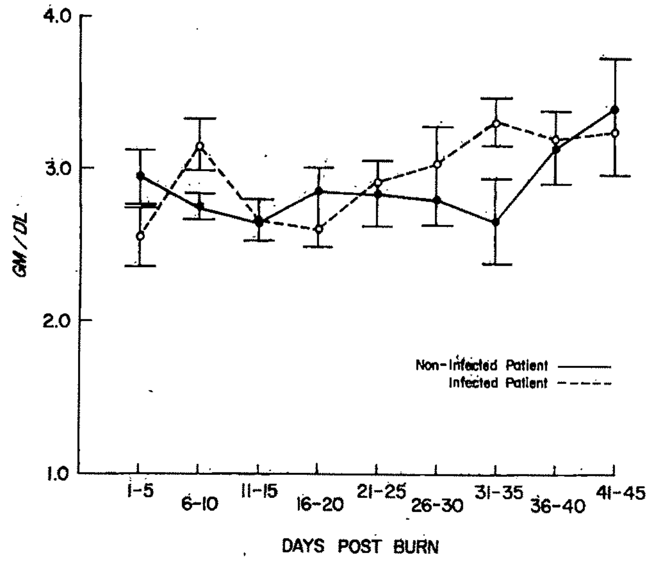

FIG. 5. Sequential analysis of serum albumin in burn patients. Values shown are the mean ± S.E.; the normal range of albumin is 3.5–5.0 gm/dl. No consistent, significant differences are seen between noninfected and infected patients.

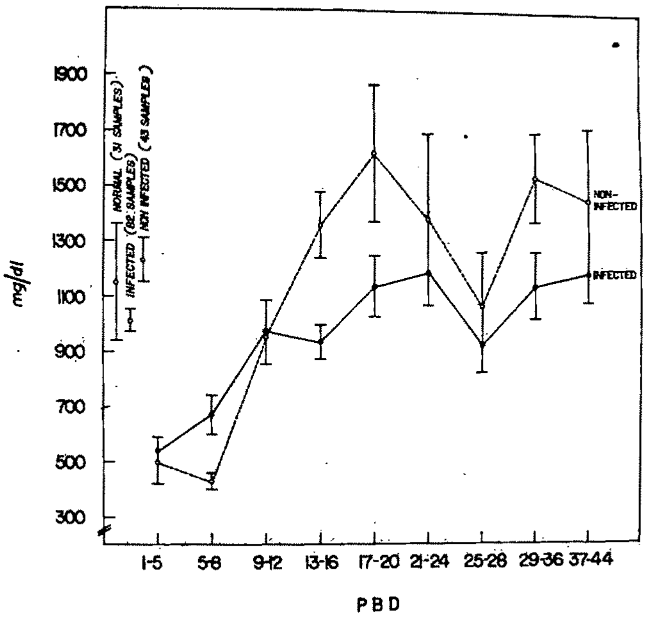

FIG. 6. Sequential analysis of IgG in burn patients. Values shown are the mean ± S.E.; normal values are 1148 ± 206 mg/dl.

Circulating levels of C3(B) increased in the serum of patients associated with 12 episodes of bacteremia and

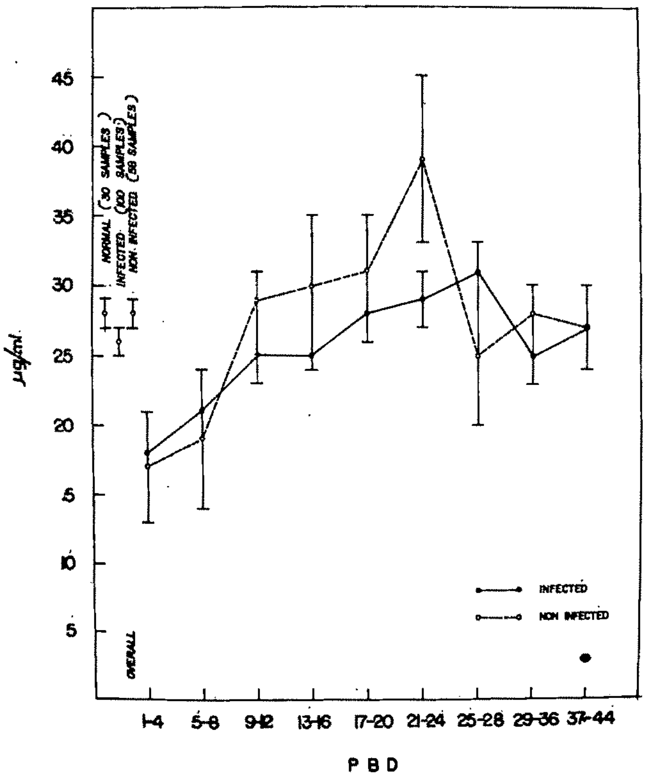

FIG. 7. Sequential analysis of properdin in burn patients. Values shown are the mean ± S.E.; normal values are 28 ± 1 μg/ml.

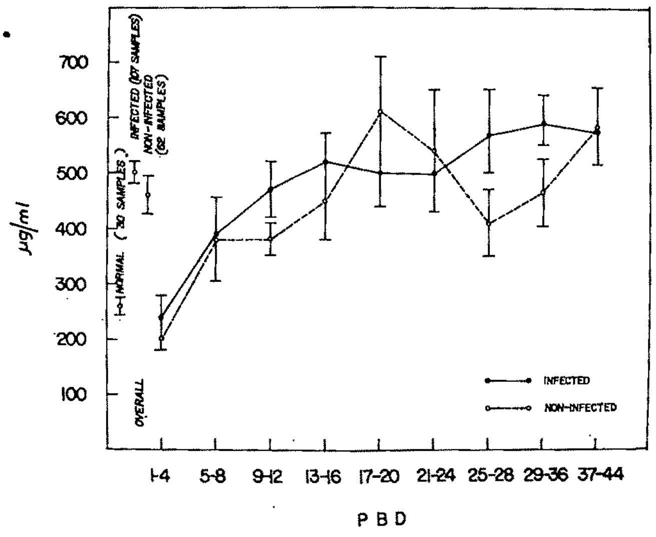

FIG. 8. Sequential analysis of factor B in burn patients. Values shown are the mean ± S.E.; normal values are 261 ± 15 µg/ml. Note the rapid rise of factor B, suggesting that this component is an acute phase protein.

fell during six episodes. In all of these last six episodes, there was also a fall in the opsonic index, but the opsonic index fell in six other patients without reduction in C3(B). Factor B rose during nine episodes of infection, fell during eight, remained unchanged in one, and was not determined in one. Properdin levels increased during ten episodes, fell during five episodes and remained unchanged during one episode. Sufficient data were not available for three episodes. Strong evidence for consumption (a drop of ≥50% in C3B and opsonic index) occurred in three patients with suggestive evidence (drops of 25–49%) in two others. In one instance properdin and factor B seemed to be involved in a consumptive process (patient 8-2).

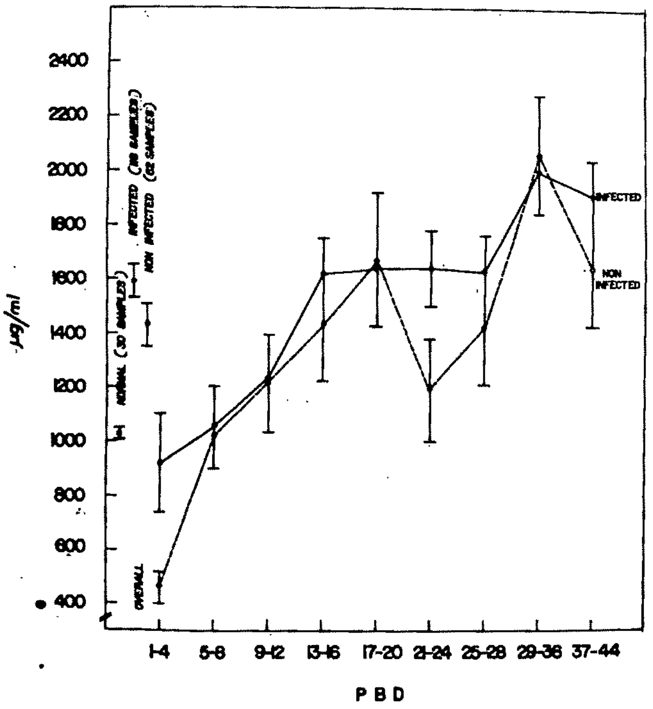

FIG. 9. Sequential analysis of C3(B) levels in burn patients. Values shown are the mean ± S.E.; normal values are 1030 ± 23 µg/ml. Initial levels are low, but rise to elevated values by the second week.

Discussion

It is well known that the antibacterial function of neutrophils, the opsonic activity of serum, lymphocyte function and function of the reticuloendothelial system (RES) all contribute to resistance to bacterial infections in experimental animals and man. All of these immunologic functions have been shown to be abnormal following burn injury.[1] However, no previous study has investigated the significance of isolated immunologic deficiencies relative to other variables of host defense against infection. We have attempted to examine those variables which were potentially of critical importance, except for function of the RES which was excluded from consideration because adequate tests for sequential evaluation in man are not currently available. The results of this study strongly suggest that acquired abnormalities of neutrophil function, measured by the ability to kill *S. aureus* 502A, are of major and primary importance in the development of bacteremia following major thermal injury. Increased susceptibility to infection associated with abnormalities of neutrophil function against *S. aureus* are in

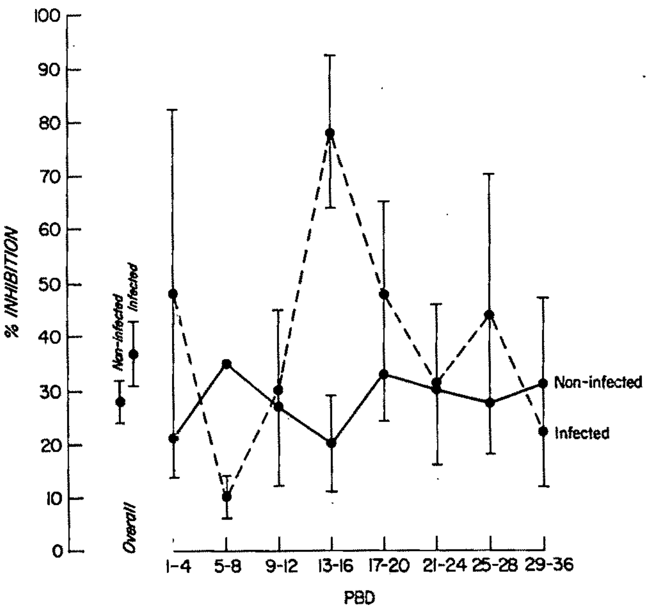

FIG. 10. Sequential analysis of the inhibition of lymphocyte PHA responses by patient serum. Values shown are the mean ± S.E.; normal serum always inhibited PHA responses less than 5%. No consistent, significant differences in serum inhibitory activity between infected and noninfected patients is apparent.

TABLE 1. *Relationship of Immunologic Variables to Bacteremia*

Patient and Episode	Organism	Preinfection*						Postinfection						Evidence for Consumption
		NBI	Opsonic Index	C3(B) μg/ml	Factor B μg/ml	Properdin μg/ml	IgG mg/dl	NBI	Opsonic Index	C3(B) μg/ml	Factor B μg/ml	Properdin μg/ml	IgG mg/dl	
1-1	S. aureus	5.0	0.31	1404	960	N.D.†	1635	N.D.	0.94	2691	870	N.D.	1635	No
2-1	S. aureus	9.9	0.89	1697	480	27	1369	N.D.	0.58	2340	495	35	1495	No
3-1	E. cloacae	16.7	0.56	1638	375	45	960	12.6	0.46	1872	450	27	624	No
3-2	S. aureus & E. cloacae	>20.0	0.96	1755	300	19	639	11.9	1.02	2574	420	38	1200	No
4-1	S. aureus	<1.0	0.88	2106	420	24	996	17.8	0.67	1170	450	27	1023	Mild
4-2	S. aureus	6.9	0.42	1580	375	39	802	3.9	0.78	1591	360	N.D.	870	No
5-1	S. aureus	5.1	0.85	1006	495	41	1194	8.1	<0.10	971	420	35	984	Yes
6-1	K. pneumoniae	8.3	0.56	1404	450	22	805	7.6	0.41	1989	450	26	805	No
7-1	E. cloacae	13.6	0.95	1755	495	24	662	>20.0	0.83	2106	420	27	723	No
7-2	S. aureus	9.3	1.05	2340	600	32	1146	3.9	0.88	1755	840	32	1528	Mild
8-1	S. aureus	N.D.	0.56	1112	630	26	960	7.7	0.99	1755	900	27	N.D.	No
8-2	Candida	2.3	1.05	2340	750	27	537	2.5	0.47	1170	630	8	480	Yes
9-1	S. aureus	2.0	0.73	702	750	16	840	2.0	0.56	1100	570	27	1026	No
10-1	Bacillus	9.8	<0.10	1170	150	27	600	6.2	1.25	1872	270	8	441	No
10-2	S. aureus	9.2	1.14	1638	315	22	1260	4.3	0.82	1521	420	27	1500	No
10-3	S. aureus	4.3	0.82	1521	420	27	1500	4.4	1.25	2457	294	24	1396	No
11-1	P. aerug.	<1.0	0.64	1112	435	14	1400	3.5	0.98	1170	420	20	1062	No
12-1	S. aureus	8.0	1.14	1755	210	25	823	4.1	0.19	410	420	28	1253	Yes
13-1	Strep.	4.0	0.88	1521	N.D.	25	1600	DIED						

* Preinfection values are from tests done on the nearest test day preceding a positive blood culture (1–4 days, av. 2.1 days). Post-infection values were from the nearest test day following a positive blood culture (1–4 days, or 2.4 days). †N.D. = not done or unable to retest because of small serum samples.

agreement with our previous findings[3,4] and those of Grogan and Miller.[10] Interestingly, the ability of neutrophils to kill *E. coli* failed to correlate with either the onset of infection or their ability to kill *S. aureus*. This dichotomy suggests different pathways of intracellular killing for these two organisms, but the apparent lack of correlation between infection and killing of *E. coli* by neutrophils remains unexplained. In this study we did not attempt to differentiate between uptake and intracellular killing defects, since our previous studies have shown that the defect in burn neutrophils is limited to intracellular killing.[3] Similarly, defective chemotaxis of burn neutrophils was, usually found in keeping with the reports of Warden et al.[24] and Grogan,[9] but this did not correlate well with the onset of infection. Warden et al.[24] have reported that continued depression of chemotaxis was highly predicative of death.

In agreement with previously reported studies,[5,15,20] circulatory levels of IgG fell significantly during the first week after injury in most patients. Overall, levels of C3 were significantly depressed in some patients during the first week, similar to the findings of Daniels et al.[6] C3 levels tended to parallel opsonic activity, but the two variables were not always concordant. Defective opsonic activity of serum for *E. coli* was associated with the onset of infections in seven instances, and five of these also had poor neutrophil function. In contrast to the findings of Weinstein and Young[25] who reported defects in opsonization of patient serum against the infecting organism in medical patients with septicemia, we could detect no instance in which defective opsonization occurred which was specific for the infecting organism. However, that study dealt only with patients with gram-negative bacteremia (predominately *E. coli*) with normal or elevated white counts. Unfortunately for our study, such infections are presently rare in our burn units. We did find evidence for a consumptive reduction of opsonic proteins in five of the 19 episodes of bacteremia, supporting our previous postulates concerning consumptive opsoninopathy.[2] C3 and factor B appeared to act as acute-phase proteins, usually increasing in concentration as a consequence of infection except where a consumptive process occurred.

The normal or increased response of isolated lymphocytes to PHA in this study is consistent with published data of Daniels et al.[7] and Leguit et al.[14] and the inhibition of lymphocyte responsiveness is in agreement with the findings reported by Munster et al.[19] and Hakim.[11] However, in our patients there was no correlation between bacteremia and the level of activity of the nondialyzable inhibitor.

It is an important observation that all but one episode of bacteremia were associated with one or more pre-existing abnormalities of immunologic defense involving neutrophil function or serum opsonins (or activity). In this patient the episode was very transient and associated with a debridement procedure.

During the past decade, there has been a remarkable decrease in mortality from septicemia and/or burn wound sepsis following major thermal injury.[1] In our units, this improvement occurred abruptly when a program of intensive oral nutritional supplementation was instituted. At the same time, there has been an overall improvement in neutrophil function in seriously burned patients. In a previous study[3] the average NBI for 33 patients with burns (average 53.6% total/39.2% 3°) having episodes of bacteremia was 9.1 compared to an average NBI of 6.8 in infected patients in the present study. In 15 nonbacteremic patients in the previous study, the average NBI was 5.8 compared to 3.8 in the present study. Levels of IgG and C3 are also higher in our current patients than in patients reported previously who were not treated with aggressive oral hyperalimentation.[5,6,15,20] Significant abnormalities in host defense have been shown to occur in malnutrition[13,23] and the elevated nutritional requirements in seriously burned patients not treated by aggressive nutritional support is well documented.[22,26] One might suspect that a major and perhaps the primary cause of acquired abnormalities of immunologic defense following burn injury is malnutrition.

While improved in comparison to previous studies, disorders of neutrophil function, which persist in currently treated burn patients, appear to be the major predisposing factors to the development of sepsis. This problem, more than any other, needs to be addressed in future studies.

Acknowledgments

The excellent technical assistance of Marlene White, R.N., Romaine Krummel, R.N., Mary Ann McClellan, B.S.N., Michael Morris, B.S., Linda Brockett, B.S. and Kenneth Kozak, B.S. are gratefully acknowledged.

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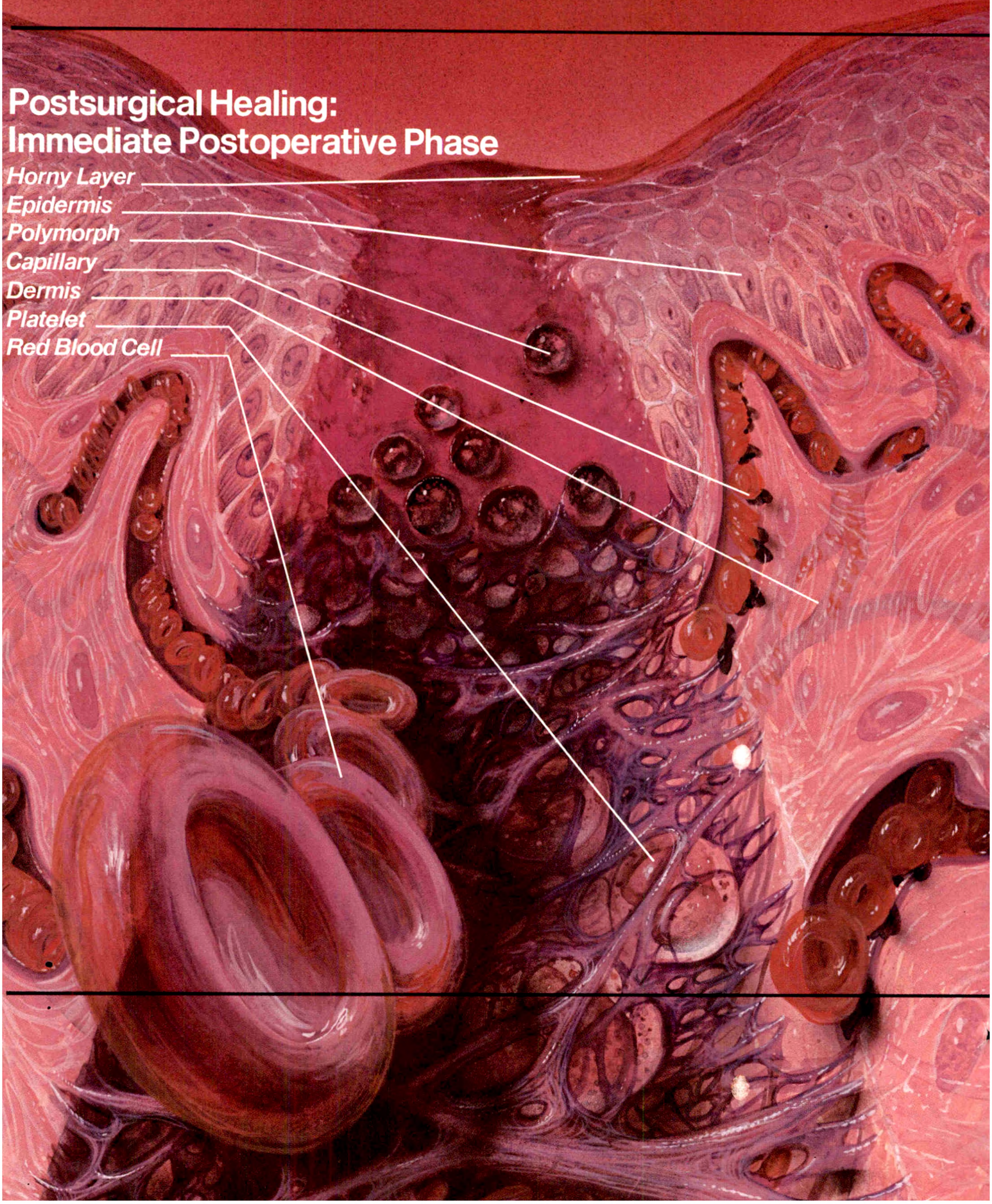

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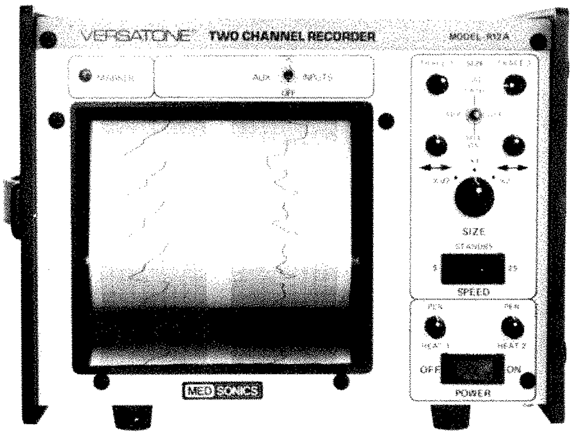

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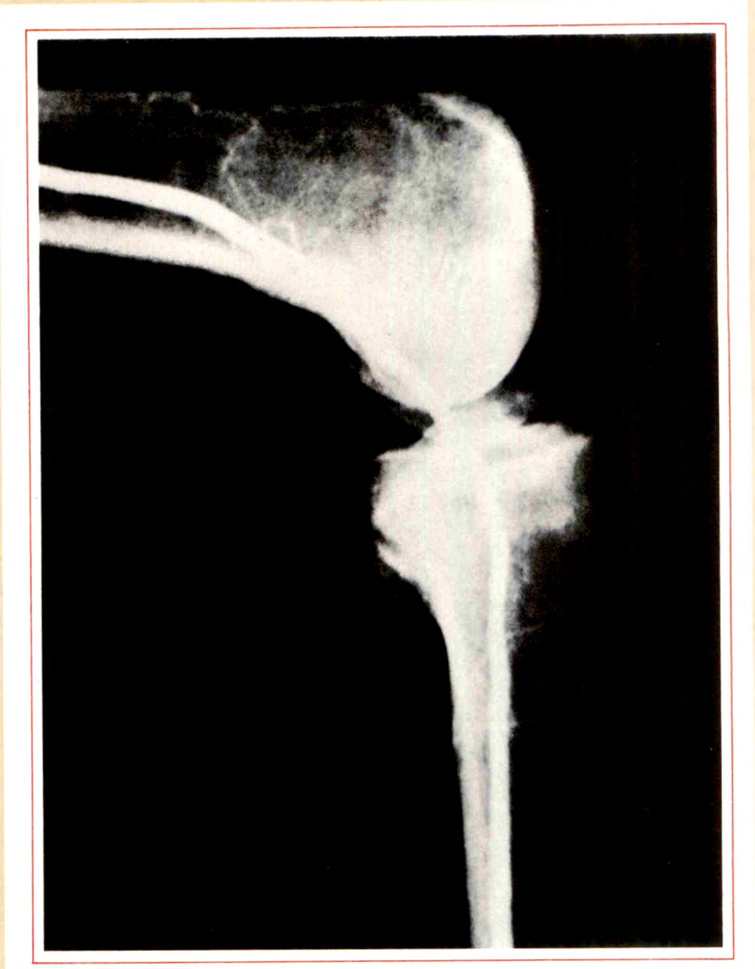

What we've learned.

Summary of Clinical Data, as of September 25, 1978.

Operation type	Number Implanted	Number Patent	% Patency	Avg. Months Weighted Experience	Months Maximum Experience
Above-Knee					
Fem-pop	1740	1526	88%	3.6	34
Ilio-fem	153	145	95%	4.1	22
Ilio-pop	58	54	93%	2.1	18
Fem-fem	105	98	93%	2.3	20
Pop-segmtl	14	11	79%	1.3	17
Aorta-pop	21	16	76%	2.4	14
Aorta-fem	133	128	96%	6.4	29
Axil-fem	143	132	92%	1.7	14
Axil-bifem	31	31	100%	3.7	16
Aorto-iliac	5	5	100%	2.0	6
Fem-profunda	14	11	79%	1.9	15
Axil-pop	19	17	89%	5.5	16
Iliac-fem	2	1	50%	3.5	7
Iliac-pop	10	7	70%	6.0	24
Others	4	2	50%	<0.5	1
Group Totals	2452	2184	89%	3.6	34
Below-Knee					
Fem-dist-pop	958	792	83%	3.2	34
Fem-ant-tibial	183	129	70%	1.5	19
Fem-post-tibial	292	197	67%	2.6	38
Fem-peroneal	111	78	70%	1.7	22
Aorta-ant-tib	2	1	50%	0.0	0
Ileo-post-tib	5	4	80%	1.2	6
Ileo-pop	5	3	60%	3.0	5
Fem-dorsalis ped	24	13	54%	3.0	12
Aorto-dist pop	5	5	100%	4.8	7
Iliac ant-tib	4	4	100%	3.2	8
Axil-dist-pop	2	2	100%	11.0	13
Iliac-dist-pop	4	2	50%	0.5	1
Pop-post-tib	2	2	100%	0.5	1
Other	7	3	43%	<0.5	1
Group Totals	1604	1235	77%	2.8	38
Cross-over Grafts					
Fem-fem	185	176	95%	6.2	30
Fem-pop	37	33	89%	2.2	24
Fem-profunda fem	3	3	100%	2.3	7
Axil-fem	6	6	100%	3.0	16
Fem-distal pop	1	1	100%	7.0	7
Others	4	3	75%	<0.5	2
Group Totals	236	222	94%	5.4	30
Composite Grafts					
C-fem-distal-pop	9	9	100%	2.6	8
C-fem-ant-tib	3	3	100%	6.0	7
C-fem-post-tib	14	13	93%	3.6	7
C-fem-peroneal	4	4	100%	2.5	5
Group Totals	30	29	97%	3.4	8
AV Fistulae	496	416	84%	3.2	22
Forearm	504	478	95%	0.8	18
Upper arm	370	352	95%	3.6	20
Arm	49	39	80%	0.7	10
Leg	101	98	97%	1.0	18
Group Totals	1520	1383	91%	2.3	22
Pulmonary Grafts					
Aorta-pulm shunt	57	48	84%	3.4	27
Pulm reconstrts	3	2	67%	0.0	0
Subclav-pulm	1	1	100%	1.0	1
Group Totals	61	51	84%	3.1	27
Other Arterial Grafts					
Renal artery	18	17	94%	10.7	30
Axil-axil	33	33	100%	4.1	18
Carot-subclav	52	50	96%	8.9	31
Aorto-coronary	15	11	73%	2.3	17
Aorto-renal	25	23	92%	4.0	26
Others	64	62	97%	3.2	29
Group Totals	207	196	95%	5.5	31
Venous Grafts	38	34	89%	7.8	42
Patches	143	135	94%	5.0	30
Totals, All Operations	6291	5469	87%	3.2	42

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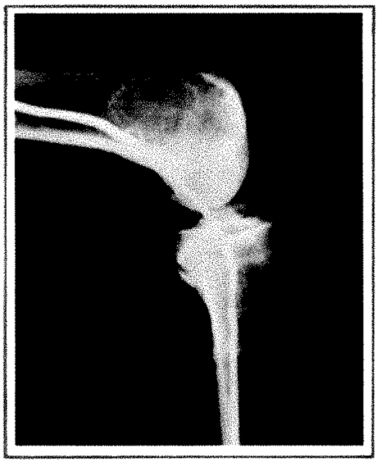
Yes, *if* there is no vein available.

Yes, *if* the vein is "borderline," either in size or condition.

Yes, *if* the patient's condition is such that a prolonged exposure to anaesthesia, or even to the delay in providing the vein, is critical.

Yes, *if* there is the likelihood of cardiac surgery, for which the saphenous vein should be saved.

Given those indications, the GORE-TEX graft is, indeed, a viable alternative to the saphenous vein. But unless those conditions exist, prudence and experience make the saphenous vein the graft of choice.



Arteriogram of a GORE-TEX polytetrafluoroethylene graft during flexion of the knee.

The problem of proof.

As of September 25, 1978, there were approximately 60,000 GORE-TEX vascular graft implants, with over 6,000 follow ups. The overall patency rate was 87%.

Those data, sliced into what we hope are useful pieces, are presented in Table at left.

A close look at the data will reveal one problem: average follow-up times.

They're too short.

The problem is two-fold.

First, we are, of course, dependent on the voluntary cooperation of surgeons for our follow-up data. And we know that if you were to provide all the data that all manufacturers wanted, you would have to spend all of your hours filling out follow-up forms. And, of course, even if you had the time, you can't keep up with all patients over a period of years.

The second part of the problem is statistical. The use of GORE-TEX grafts is increasing so rapidly that we will, for a long time to come, have a far greater number of recent implants than of old ones. (For every GORE-TEX graft implant used three years ago, there are almost 100 used today. Our current reported rate-of-use is approximately 5,000 per month.)

This necessarily skews our data average toward the more recent history. Which is also true for a life table method of data presentation. Even though the maximum experience reported in each category is in the two-to-three *year* range, the weighted averages are more like two-to-three *months.*

More data. More problems. Some suggestions.

On the last page of this advertisement, you'll find a bibliography of published experimental and clinical reports on the use of GORE-TEX vascular grafts, and a coupon for your convenient use.

One problem is that we know the list is not current. Additional papers are always being delivered, and published. If you would like us to keep you up-to-date as new reports appear, check the appropriate box on the coupon.

A more basic problem with these data, and ours, and *all* vascular statistics is the lack of uniformity in reporting. We're supporting efforts to establish some profession-wide protocols begun with a symposium at the 1978 meeting of the American College of Surgeons. If you have any suggestions at all, we'd appreciate them. Just write to us.

GORE-TEX® vascular grafts, in brief.

GORE-TEX vascular grafts are made of expanded, low-density polytetrafluoroethylene (PTFE), reinforced by a strong, fine lattice of the same material wound about the exterior.

GORE-TEX vascular grafts are easy to handle, with excellent resistance to kinking. And they exhibit high suture-holding power. They are, of course, fully biocompatible and, unlike knitted or woven prostheses, do not require pre-clotting.

GORE-TEX vascular grafts for vascular surgery are available in a wide range of diameters.

See next page for free GORE-TEX graft test-pack and complete bibliography, available as reprints.

Free test-pack, reprints.

Submit the handling and suture-holding characteristics of GORE-TEX grafts to the most meaningful test equipment: your own hands. Our test kit, not intended for actual surgery, includes a short length of a GORE-TEX graft and a 6-0 double-armed suture. Try it for yourself. Also, take your choice of reprints of any of the experimental, clinical, and engineering reports listed.

Current bibliography.

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13. **A New Vascular Prosthesis for Small Caliber Artery** H. Matsumoto, M.D., T. Hasegawa, M.D., K. Fuse, M.D., M. Yamamoto, M.D., M. Saigusa, M.D. *Surgery* October, 1973
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15. **Summary of Clinical Evaluation Data,** May, 1977 *W. L. Gore & Associates, Inc.*
16. **Long-Term Dilatation Characteristics of GORE-TEX Vascular Grafts: Design Criteria** *W. L. Gore & Associates, Inc.*

Indications and Contraindications.

To sterilize:
Grafts may be sterilized using steam, gas or flash autoclave techniques. Remove the graft from the PVC blister tray and repackage for sterilization. Do not place the package label in contact with the graft during sterilization. Do not place objects on the repackaged graft during sterilization. (See Contraindication #5, 6)

Using steam, autoclave at or above these minimum requirements: 250° Fahrenheit (121° Centigrade) for 20 minutes at 15 p.s.i. Grafts should never be exposed to temperatures greater than 482° Fahrenheit (250° Centigrade).

Using a flash cycle, sterilize at or above these standard minimum requirements: 270° Fahrenheit (132° Centigrade) for 3 minutes at 30 p.s.i. Grafts should never be exposed to temperatures greater than 482° Fahrenheit (250° Centigrade).

Using gas, sterilize according to equipment instructions.

Indications:

1. Use a 5-0 or 6-0 nonabsorbable suture with a cardiovascular needle for best results on graft diameters of 6mm or less. Larger sutures may be used with larger diameter grafts.
2. Intra-operative inspection of anastomoses using irrigant solutions may result in serum leakage when blood flow is established in the graft. To prevent this, care must be taken not to generate syringe pressures sufficient to force irrigant through the graft walls. To do so will alter the hydrophobic (non-wetting) properties of GORE-TEX. (See Contraindication #11)
3. Trim grafts to desired length using sharp surgical instruments. Grafts should be handled with clean forceps or gloves. GORE-TEX grafts are not "elastic." Therefore, proper matching of lengths is essential. If the graft is cut too short, excessive stress may be placed on the sutures and the graft at the anastomosis. (See Contraindication #10)
4. Ensure, when using this graft in blood access applications or where repeated needle punctures of the graft are necessary, that needle puncture sites are spaced apart along the accessible sub-cutaneous length of the graft. Repeated needle puncture of the graft at the same site, or within the same immediate area, may cause mechanical damage to the graft which could lead to hematoma, false aneurysm or true aneurysm. Patients should be carefully monitored to assure that this instruction is followed.

Contraindications:

1. Do not pre-clot the graft.
2. Do not sterilize by irradiation techniques.
3. Grafts should never be exposed to temperatures exceeding 482° Fahrenheit (250° Centigrade).
4. Do not sterilize more than three times.
5. During sterilization, do not place grafts under heavy or sharp objects which might crush the grafts.
6. Do not attempt to sterilize the label attached to the PVC blister tray at high temperatures, as the materials (inks and adhesives) on the label may contaminate any objects in contact with the label during the sterilization cycle.
7. Do not handle graft with ungloved hands. It should be handled only with clean instruments.
8. Do not attempt to resterilize any unused graft portion which has been contaminated with blood or any other foreign material.
9. Do not use absorbable sutures.
10. Do not cut graft while holding under tension. Doing so may cause separation of the outer layer. The GORE-TEX graft is a composite structure consisting of an inner base tube and a thin outer layer which reinforces the base tube to prevent aneurysmal dilatation. Do not use any portion of a GORE-TEX graft which has damage to or separation of the outer layer of the graft.

    Should the outer reinforcing layer become frayed at the end of the graft, do not pull on or peel the outer layer from the base tube. Carefully trim off the portion of the graft where the outer layer is frayed.
11. Do not force irrigating solutions through the graft wall. Doing so may result in serum leakage after blood flow is established.
12. Do not place grafts in any fluid prior to use. Doing so may result in serum leakage after blood flow is established.
13. Do not puncture the graft repeatedly at the same site, or within the same immediate area. (See Indication #4)

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The major toxic effect of parenterally administered kanamycin sulfate is its action on the auditory portion of the eighth nerve. High frequency deafness usually occurs first and can be detected by audiometric testing. Tinnitus or vertigo may occur and are evidence of vestibular injury and impending bilateral irreversible deafness.

In patients with impaired kidney function, the risk of severe ototoxic reactions and permanent deafness is sharply increased. In such cases, the daily dosage should be reduced and the interval between doses lengthened. If there is evidence of progressive renal dysfunction (increasing NPN, BUN, creatinine or oliguria) during therapy, audiometric tests are advised and discontinuation of the drug should be considered.

Older patients and patients receiving a total dose of more than 15 Gm. of kanamycin sulfate should be carefully observed for signs of eighth nerve damage.

Infants and children generally tolerate the drug well; and when the recommended precautions are followed, the incidence of toxic reactions is low.

Neuromuscular paralysis with respiratory depression may occur when kanamycin sulfate is administered intraperitoneally concomitantly with anesthesia and muscle-relaxing drugs. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug.

The concurrent systemic use of other ototoxic and/or nephrotoxic drugs, particularly streptomycin, polymyxin B, polymyxin E (colistin), neomycin, gentamicin, and viomycin should be avoided.

The administration of kanamycin sulfate and rapid acting diuretic agents, e.g. ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, and mannitol (particularly when the diuretic is given intravenously) may cause irreversible deafness. Concurrent use of these agents should be avoided. (See "Adverse Reactions".)

Usage in Pregnancy
Safety of this drug in human pregnancy has not been established.

CONTRAINDICATIONS:
A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other potentially ototoxic agents may be a contraindication if effective, alternative therapy is available.

THIS DRUG IS **NOT** INDICATED IN LONG-TERM THERAPY (e.g. Tuberculosis) BECAUSE OF THE OTOTOXIC HAZARD WITH EXTENDED ADMINISTRATION.

WARNING:
See "Warning" box above.

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Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occurs, discontinue therapy. Mycotic or bacterial superinfection may occur.

ADVERSE REACTIONS:
Nephrotoxicity—albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity—see box warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

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"Kanamycin has been employed in 128 patients at the time of operation for intraperitoneal contamination of various types. There has been no evidence of toxicity from this use of kanamycin." —Cohn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

"Wider usage of intraperitoneal kanamycin is advocated when intraperitoneal antibiotic therapy is indicated." —Cohn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

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"Intraperitoneal kanamycin therapy is strongly advocated for any patient with peritonitis." —DiVicenti, F.C., and Cohn, I., Jr.: Am. Journ. Surg. 111:1, pages 147-153, (June) 1965.

"In peritonitis, intraperitoneal administration of kanamycin can be recommended..." —Pissiotis, C.A., et al.: Surg. Gynecol. Obstet. 134:995 (June) 1972.

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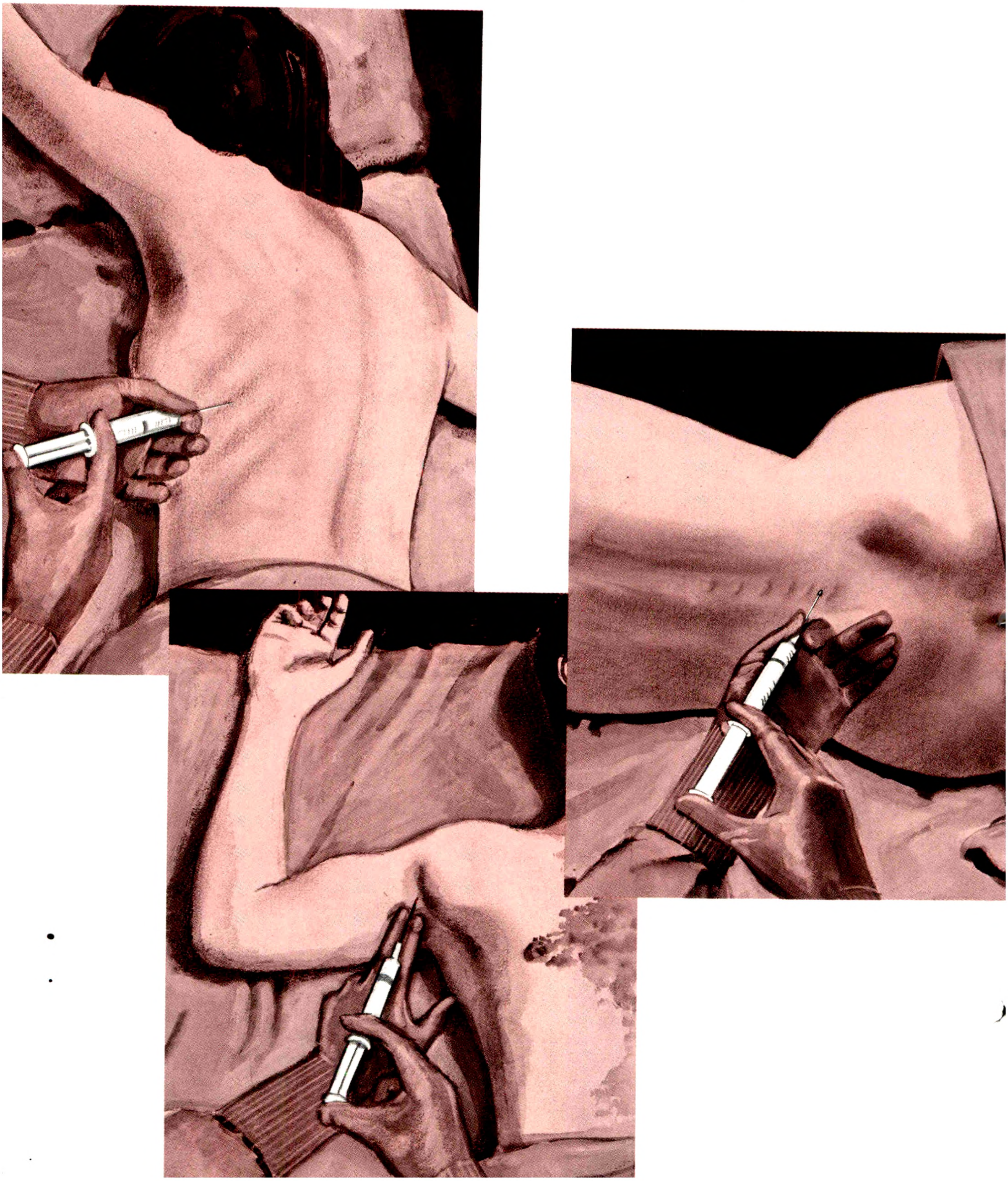

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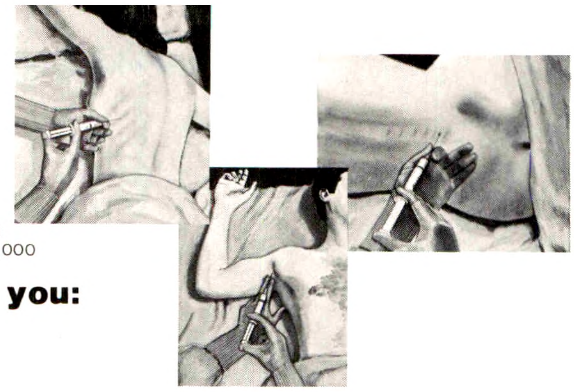

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Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

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FORMULA

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0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.50	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.50	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						0.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

Autogenous Profundaplasty:

The Key to Long-term Patency in Secondary Repair of Aortofemoral Graft Occlusion

JAMES M. MALONE, M.D., JERRY GOLDSTONE, M.D., WESLEY S. MOORE, M.D.

The records of 281 patients undergoing aortic grafting to 522 femoral arteries over a period of 18 years were reviewed. Fifty-four patients suffering graft limb occlusion to 71 femoral arteries requiring subsequent secondary repair were identified for detailed analysis. Occlusive disease of the profunda femoris artery was identified as the primary cause of thrombosis. Repair consisted of profunda femoris angioplasty, and transfemoral retrograde graft thrombectomy was possible in all but three instances which were managed by cross-over femoral–femoral bypass. In no instance was laparotomy and abdominal graft replacement necessary. The 30 day operative survival and graft patency were 100%. Analysis of factors that have influenced late graft patency demonstrated that the key factors were the method of profundaplasty and the association of diabetes mellitus. When autogenous profundaplasty (on-lay arterial patches, saphenous vein, or limited endarterectomy) was employed, the overall patency combining diabetics and nondiabetics was two and one-half times greater than when profundaplasty was performed with an on-lay Dacron® patch. If diabetics were separated from nondiabetics in the autogenous angioplasty group, the 36 month patency for nondiabetics was 85%, and 0% for diabetics. We conclude that autogenous profundaplasty provides considerable advantage from the standpoint of long-term patency and that the diabetic patients are relatively poor candidates for secondary arterial repair of an occluded aortofemoral bypass graft.

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LATE GRAFT OCCLUSION following aortofemoral reconstruction may be caused by initial technical error, progression of atherosclerotic occlusive disease involving outflow branches, graft infection, anastomotic aneurysm formation, or defects in the prosthetic graft material leading to disruption. Most of these causes of failure are preventable at the time of implantation with the exception of progression of atherosclerosis. While it may not be possible to prevent progression of atherosclerosis following bypass grafting, recent observations have led us to believe that the management of the profunda femoris artery at the time of initial replacement may have a significant influence on the subsequent incidence of late graft failure due to atherosclerotic extension.

The purpose of this report is to outline the factors associated with progression of atherosclerotic lesions, evaluate prognostic factors associated with prolonged graft patency, compare patency rates following several methods of secondary arterial repair, and to emphasize the value of proper management of the profunda femoris artery at the time of primary reconstruction of the aortofemoral system.

Clinical Material and Methods of Study

The records of 281 patients who underwent aortofemoral bypass grafting at the V.A. Hospital, San Francisco, between May, 1959, and April, 1977, were reviewed. Two hundred and forty-one patients had aortobilateral femoral bypass grafts inserted, and an additional 40 patients had aortounilateral femoral bypass performed. These cases provided a total of 522 femoral graft limbs for long-term evaluation of patency. Fifty-four out of 281 patients (19%) required secondary repair for a total of 71 graft limb occlusions (13.6%). This group was evaluated in detail and constitutes the basis for analysis in this report.

All patients were men, and 100% were smokers with more than a 20 pack-year history. Ages ranged from 32 to 74 years with a mean age of 56. Patient follow-up ranged from four to 85 months, with a mean follow-up of 16 months.

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Submitted for publication: February 13, 1978.

0003-4932/78/1200/0817 $00.85 © J. B. Lippincott Company

TABLE 1. *Method of Secondary Profunda Femoris Reconstruction*

Type of Operation	Number of Graft Limbs	Per Cent
Patch profunda femoris reconstruction		
Autogenous patch	27	38
Dacron patch	40	56
Miscellaneous	4	6
	71	100

Associated Disease

Thirty-eight of 54 patients (70%) had evidence of coronary artery disease as manifested by an abnormal electrocardiogram, angina pectoris, prior myocardial infarction, or compensated congestive heart failure. Twenty-three of the 54 patients (43%) had hypertension as defined by a blood pressure greater than 150/90. Twenty-two of the 54 patients (41%) had evidence of cerebrovascular disease as manifested by prior cerebrovascular accident, a history of transient ischemic attacks, prior carotid artery surgery, or the presence of a bruit over one or both carotid bifurcations. Diabetes mellitus was present in 20 of the 54 patients (37%).

Arteriography

All patients underwent preoperative arteriography prior to the initial placement of their aortofemoral bypass grafts. Visualization of their arterial tree was achieved from the infrarenal abdominal aorta down to and including both popliteal trifurcation areas. All patients requiring secondary vascular reconstruction were similarly restudied angiographically prior to repair. Early in our series aortography was achieved by the translumbar method. However, after 1971 all patients undergoing vascular reconstruction were studied by the percutaneous retrograde transformal Seldinger technique in order to provide more detailed information regarding the iliofemoral inflow and the popliteal-trifurcation outflow. We have indicated in previous reports that oblique views of the common femoral bifurcation are necessary to provide adequate visualization of the origin of the profunda femoris artery as well as to visualize the extent of posterior plaquing in the iliac and femoral arteries.[5-7]

Operative Indications

An analysis of the 54 out of 281 patients (19%) that required secondary arterial repair of a total of 71 graft limbs (13.6%) revealed that the indications for secondary vascular reconstruction included graft limb thrombosis with recurrence of profound lower extremity ischemia in 46 of 71 graft limbs (65%). Symptoms of progressive lower extremity ischemia were present in 19 of 71 graft limbs (27%), and noninfected false aneurysms constituted the final indication in six of 71 graft limbs (8%). Fifty out of 54 patients underwent some form of profunda femoris reconstruction at the time of secondary surgical repair. Sixty-seven profundaplasties were performed in these 50 patients, for an average of 1.34 profunda femoris reconstructions per patient. In the remaining four patients various miscellaneous types of reconstruction were performed and those patients will not be part of this report (Table 1). Twenty-five of the 50 patients (50%) who underwent secondary profunda femoris reconstruction required two or more attempts at vascular repair for either recurrent graft limb thrombosis (21/25, 84%) or symptoms of progressive lower extremity ischemia (4/25, 16%).

Operative Technique

All patients requiring secondary surgical procedures who were analyzed for this report had their operations performed in our institution. The technique of primary operation is fairly standardized, and has been described in previous reports.[8,9] Most of the operations were aorto bilateral femoral bypass grafts connected in an end-to-side fashion between the graft and the aorta, and end-to-side to both femoral arteries. In our early experience we had 40 cases of aorto-unilateral femoral bypass. The unilateral operation, however, has been abandoned with the recognition that even in the absence of symptoms on the contralateral side there is usually sufficient disease to require bilateral operation in order to avoid occlusive complications associated with the unoperated side.

For the secondary surgical repair, the patients were operated upon under general anesthesia. The abdomen, both groins, and both lower extremities were prepared and draped free. The femoral incision on the side of graft occlusion was reopened and dissection of the graft, femoral artery, and femoral branches was accomplished using sharp dissection. The Dacron® graft was then detached from the femoral anastomosis in order to facilitate the identification of the lesion or lesions that produced graft thrombosis. In most cases the superficial femoral artery was occluded and the origin of the profunda femoris artery was either highly stenotic or occluded as well. The remainder of the profunda femoris artery, however, was usually patent. The profunda femoris outflow was reconstructed by patch angioplasty, either with or without associated thromboendarterectomy. A total of 67 profunda femoris angioplasties were performed. The patients can be divided into three subgroups corresponding to the type of material selected for profundaplasty. The first subgroup utilized a Dacron patch angioplasty for 40 profunda femoris vessels in 25 patients. The second subgroup utilized autogenous saphenous vein patch in three profunda femoris reconstructions, and the third subgroup utilized previously occluded superficial femoral artery prepared by endarterectomy and subsequent onlay patch angioplasty on 24 occasions. The total number of patients receiving profunda angioplasties utilizing some form of autogenous material constituted 25 patients. A photographic example of autogenous profundaplasty utilizing saphenous vein is shown in Figure 1, and a schematic drawing of our technique for autogenous profundaplasty utilizing ipsilateral occluded superficial femoral artery is shown in Figure 2. All patients were heparinized during the angioplastic procedures employing 1.5–2.0 mg/kg bodyweight of heparin. The total length of profunda angioplasty varied from three to fifteen centimeters, depending upon the extent of profunda femoris occlusive disease. Most patch angioplasties were constructed over a 10–14 French irrigating catheter which was inserted into the distal profunda femoris artery during the reconstruction and permitted the installation of heparinized saline into the distal arterial tree. The majority of patients had a concomitant common femoral endarterectomy in association with the profunda patch angioplasty. The common femoral artery was usually divided in anticipation of performing an end-to-end anastomosis between the reconstituted graft and the newly constructed profunda femoris outflow. Upon completion of profunda angioplasty and prior to femoral artery anastomosis, an intraoperative arteriogram was obtained to assure satisfactorily reconstructed outflow. An example of a postautogenous profunda femoris reconstruction arteriogram is shown in Figure 3. The technique of graft thrombectomy has been previously described.[1-4] Basically, a retrograde thrombectomy employing a Fogarty thrombectomy catheter is satisfactory in restoring arterial inflow through the recently occluded graft. If it is necessary to free adherent pieces of neointima or adherent thrombus from the graft surface, an endarterectomy stripper can be passed over the Fogarty embolectomy catheter and this instrument used to scrape free the adherent material. Once satisfactory thrombectomy has been achieved and arterial inflow restored to a satisfactory level, a retrograde arteriogram is performed through the graft to assure adequate extraction of existing thrombus. A anastomosis between the graft and the femoral artery is then achieved using a continuous 4-0 braided Dacron suture.

FIG. 1. Intraoperative photograph demonstrating profundaplasty which employed an on-lay saphenous vein patch.

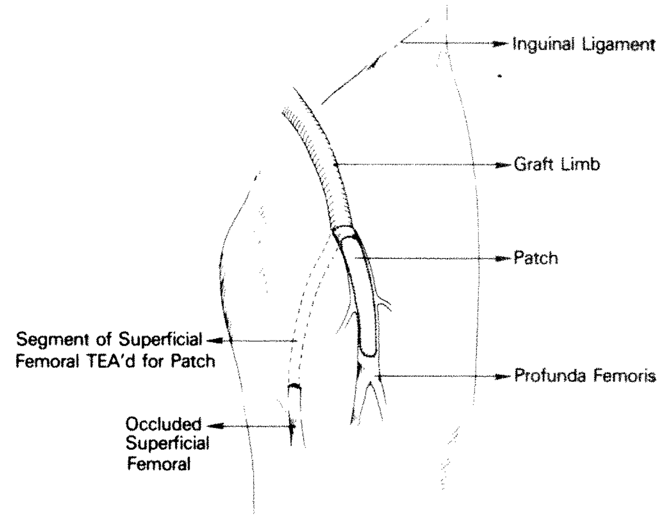
Inguinal Ligament
Graft Limb
Patch
Segment of Superficial Femoral TEA'd for Patch
Profunda Femoris
Occluded Superficial Femoral

FIG. 2. Schematic diagram for utilization of an endarterectomized segment of occluded ipsilateral superficial femoral artery as an on-lay patch profundaplasty, left groin.

In only three cases (3 of 71, 4%) was retrograde graft thrombectomy not accomplished. In none of these cases, however, was transabdominal aortofemoral graft revision required. In all three cases cross-leg femoral-to-femoral grafts were utilized, with an end-to-side anastomosis from the contralateral femoral graft limb (inflow) and an end-to-end anastomosis to the reconstituted common femoral/profunda femoris artery.

Methods of Data Analysis

No attempt was made in this series of patients to randomize profunda reconstructions for the purpose of comparison of autogenous and Dacron profundaplasties. Dacron profundaplasty was our initial method of profunda femoris reconstruction, and autogenous profundaplasty was introduced more recently. As we followed these patients, it appeared

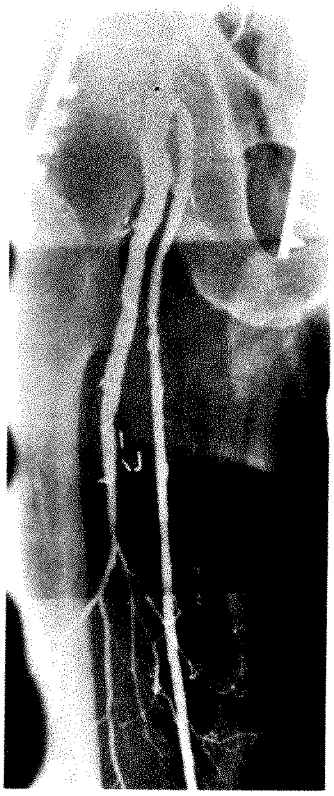

FIG. 3. Postreconstruction arteriogram 15 cm saphenous vein on-lay patch profundaplasty, right groin.

that those patients in whom autogenous profundaplasty was utilized had better long-term patency. We converted our standard operative technique, therefore, to autogenous profundaplasty and have utilized that method for the last three years. This report constitutes our first retrospective analysis of the data.

The clinical information was obtained by review of the patients' medical records and by return physical examination on all living patients. Data were recorded on punch index cards and hand sorted for purposes of correlative analysis. All calculations were performed on a programmable electronic calculator. Patency data, symptomatic status, and limb salvage were expressed in a life table format, as previously described.[7,8] In order to permit data evaluation of patients having undergone unilateral operations together with those having had aorto bilateral femoral bypasses, data were tabulated on the basis of individual graft limbs rather than patients.

Statistical correlation was obtained by chi square analysis with 2 × 2 contingency tables, corrected for continuity.

Results

The operative mortality for the group of patients undergoing secondary surgical repair was 0% for 30 days. By the time of this review, eight of 50 patients (16%) died. Seven of eight late deaths were due to myocardial infarction, and one death was due to sepsis unrelated to vascular reconstructive surgery. The cumulative 5 year life table survival was 52%.

Success of revascularization as indicated by immediate graft limb patency was 100% in this group of patients. If one looks at the entire series as a group, however, the cumulative graft limb patency, expressed in a life table format, was only 2% at 36 months (Fig. 4). However, if one divides the over all group into those patients having autogenous profundaplasty versus those having dacron profundaplasty, the cumulative 36 month patency rate was 30% for the autogenous profundaplasty subgroup, and 0% for the Dacron profundaplasty subgroup (Fig. 5). The 50% thrombosis rate prevailed at seven months in the dacron subgroup, but did not occur until 17 months following autogenous reconstruction. Thus autogenous reconstruction is associated with a 2.5× increase in cumulative graft limb patency when compared to Dacron profunda reconstruction. The differences in cumulative patency and 50% failure rate between autogenous and Dacron profundaplasty are statistically significant (p = 0.001).

Figure 4 compares the overall patency for those pa-

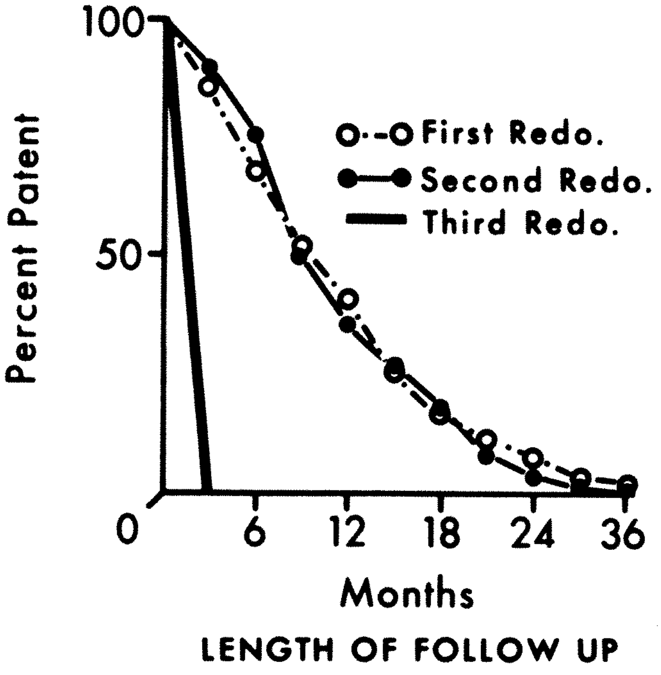

FIG. 4. This is a life table representation expressing cumulative patency of femoral limb reconstruction following profundaplasty in each of three groups, following first, second, and third secondary reconstruction. The longevity of patency after the first and second attempts at revascularization are essentially identical with the 50% thrombosis rate occurring at about 11 months. This is in marked contrast to the longevity of patency following the third attempt at secondary repair, all of which rethrombosed by three months.

tients having one, two, and three or more secondary reconstructions. It should be noted that the cumulative patency rates for the combined series are identical for the first and second reconstruction; however, no patient who underwent three or more secondary profunda femoris reconstructions had a patent graft longer than three months. There are no significant differences between the cumulative patencies of the first and second redo operations; there is a statistically significant difference, however, in late patency when one compares the first and/or second secondary repair with the patients who went on to a third repair (p = 0.001).

If those patients undergoing Dacron profunda angioplasties are subdivided into groups based upon the presence or absence of diabetes mellitus, the 21 month patency rate following Dacron profundaplasty in the diabetic group was 0%, and in the nondiabetic group 18%; however, this difference was not statistically significant. If those patients who underwent autogenous profunda femoris reconstructions are subdivided into groups based upon the presence or absence of diabetes mellitus, the differences in patency are striking (Fig. 6). The 36 month cumulative patency rate following autogenous profundaplasty in the diabetic patient was 0%, contrasting sharply with the 85% patency rate in nondiabetic patient. This difference is statistically significant (p = 0.001). In addition, analysis of the patency curve of the nondiabetic patient undergoing autogenous profundaplasty reveals that the slope maintains a horizontal characteristic, *i.e.*, a slope of 0, between 12 and 36 months, indicating continuous patency in the group at risk.

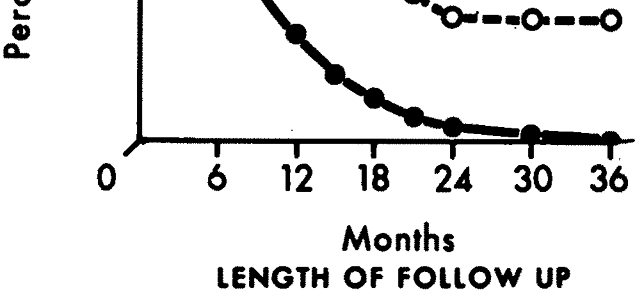

FIG. 5. This life table format contrasts femoral graft limb patency following autogenous profundaplasty and dacron profundaplasty. Autogenous profundaplasty produced a statistically improved result on long-term follow-up.

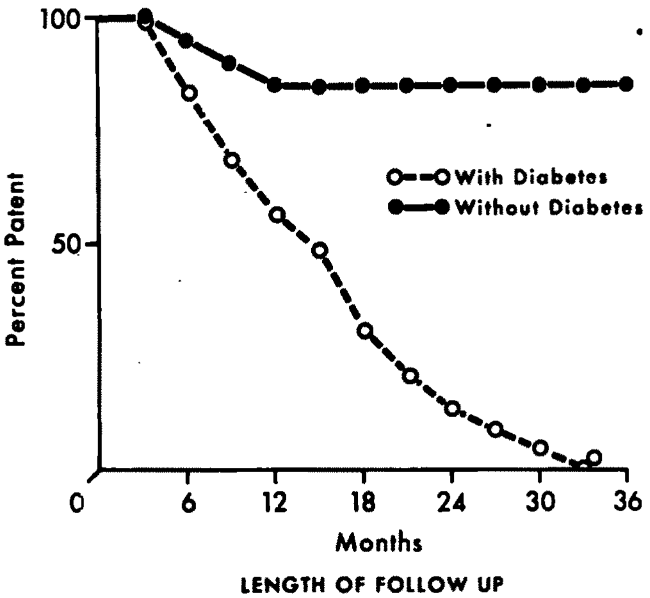

FIG. 6. This life table format contrast femoral graft limb patency in patients with and without diabetes mellitus who underwent autogenous profundaplasty. The high rate of thrombosis in the diabetic patient, in spite of autogenous profundaplasty, is in dramatic contrast to the continuous patency seen in the nondiabetic patient following autogenous profundaplasty.

Analysis of the symptomatic improvement and benefit following secondary surgical repair was accomplished by looking at the maintenance of symptom-free or symptom-improved status following surgical repair, and expressing that benefit as a function of time in a life table format. In other words, if the patient achieves a certain symptomatic improvement immediately following secondary surgical repair, the duration of that improvement before deterioration of symptomatic status occurs is defined as the interval of symptomatic maintenance. If one compares the curves for symptomatic maintenance with those of graft limb patency in the subgroups of autogenous and Dacron profundaplasty, one finds that the level of symptomatic improvement and maintenance is identical with graft limb patency. More important, however, is the fact that those patients who became totally asymptomatic following secondary surgical repair had continuous patency of their graft limbs on follow-up. In contrast, that group of patients who were only improved, but still had some symptomatic component following secondary surgical repair, experienced a fall-off of graft patency in follow-up. Therefore, the symptomatic status immediately following secondary surgical repair became an important predictor as to whether or not the patient who continue to enjoy longterm graft

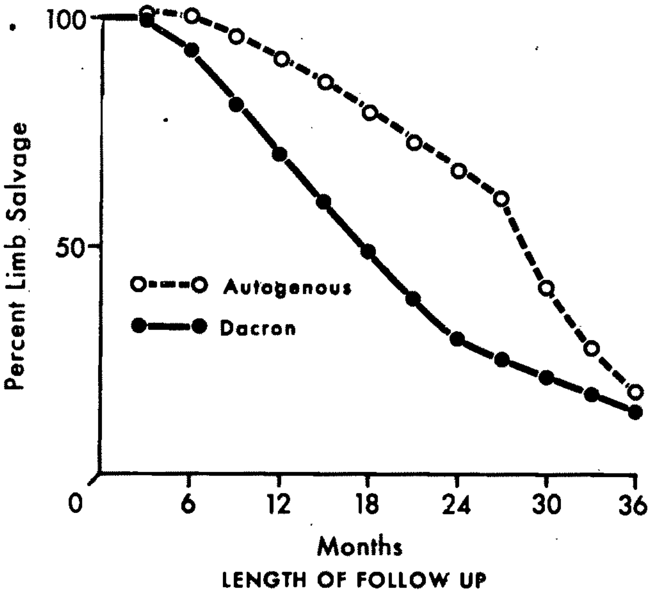

FIG. 7. Cumulative limb salvage after either autogenous or Dacron profunda reconstruction.

patency or would fall into the group of patients in whom there would be an attrition of late patency.

In those patients who had undergone the operation as a limb salvage procedure to prevent impending amputation, both the immediate and the three month limb salvage following secondary surgical repair for both Dacron and autogenous profundaplasty were 100%. The 36-month cumulative limb salvage rates for the autogenous and Dacron profundaplasties were 18% and 14% respectively (Fig. 7). However, the 50% limb salvage interval after secondary surgical repair was much longer for autogenous reconstruction (28 months) than for Dacron angioplasty (18 months).

An analysis of the angiographic data of patients undergoing their first secondary surgical repair as a predictor of late patency revealed that only one factor was important in prognosis. Those patients who had tandem lesions of both the profunda femoris and popliteal trifurcation vessels, in contrast to those patients in whom tandem lesions were not present, had a statistically higher thrombosis rate ($p = 0.05$). No other angiographic combination of lesions appears to influence the late patency of secondary surgical repair.

Discussion

The management of the profunda femoris artery is the single most important factor in long-term patency of an aortofemoral bypass graft. This is true not only for the initial operation but also for secondary surgical repair. In a previous report we demonstrated the importance of correcting all lesions of the profunda femoris artery, regardless of how minimal, at the time of initial grafting. The long-term patency rate statistically improved in contrast to those patients with minimal profunda femoris lesions that were not repaired.[8] In this report we demonstrated that occlusive disease of the profunda was primarily responsible for graft occlusion, and that autogenous repair of the profunda produced a patency rate two and one-half times greater than that of Dacron profundaplasty ($p = 0.05$). This difference is particularly impressive when comparing the diabetic with the nondiabetic subgroups. Since diabetes mellitus is often associated with an increased incidence of atherosclerotic disease of a profunda femoris artery, one would expect decreased graft limb patency in those patients with diabetes mellitus. Surprisingly, the data demonstrated equally poor graft limb patency in the diabetic and nondiabetic subgroups in those patients who had their profunda femoris arteries reconstructed with prosthetic graft material. However, analysis of those profunda femoris arteries reconstructed with autogenous tissue unmasked a good 36 month cumulative patency rate in nondiabetic patients (85%), but had no material benefit for a diabetic patient (0% patency). In addition, analysis of the patency curve of the nondiabetic patient undergoing autogenous profunda femoris reconstruction reveals that the graft limb patency curve is unaltered between 12 and 36 months, indicating continued graft limb patency in the group at risk, while in the diabetic patients who underwent autogenous profunda femoris reconstruction there were no graft limbs patent after 36 months.

Sixty-eight of 71 thrombosed graft limbs (96%) were opened by extra-abdominal retrograde thrombectomy. Only three graft limbs required inflow reconstruction. In all three cases inflow was provided from a crossover femoral–femoral bypass graft. Transabdominal aortofemoral graft revision was not used in this series. The 30 day operative mortality of 0%, the 100% immediate graft limb patency, and satisfactory cumulative graft limb patency validates the efficacy of extra-abdominal retrograde graft limb thrombectomy as compared to transabdominal aortofemoral graft reconstruction as an adjunct to secondary repair. This observation has also been corroborated by a recent report of Bernhard et al.[2]

It is of interest that the curves for both postoperative symptomatic maintenance and graft limb patency are identical ($p = 0.001$). In other words, immediate postoperative symptomatic status is a statistically reliable predictor of ultimate graft limb patency. Most important, however, is the fact that those patients who became asymptomatic following secondary arterial reconstruction had continued patency of their graft limbs on follow-up compared to those patients who were improved after secondary reconstruction but still had symptoms of arterial insufficiency. The latter group experienced a progressive decrease in graft patency during long-term follow-up.

The only angiographic pattern of disease which was associated with decreased patency after secondary arterial repair was the simultaneous occurrance of atherosclerotic lesions in both the profunda femoris artery and tibial trifurcation vessels. This is the same factor that is associated with subsequent thrombosis following primary operation.[8]

Based upon analysis of our data, it is not justified to do more than two secondary repairs for graft limb occlusion. No patient had graft limb patency exceeding three months after three or more attempts at secondary reconstruction. In those patients who were failures after two attempts at secondary reconstruction the judicious use of amputation to achieve rapid patient rehabilitation rather than continued arterial reconstructive surgery would appear to be warranted.

Seventy-one of 522 graft limbs (13.6%) following either aortounilateral or aortobilateral femoral bypass grafting required secondary vascular reconstruction for either increasing symptoms of peripheral vascular ischemia or graft limb thrombosis. Our incidence of graft limb occlusion is slightly higher than that reported by either Najafi et al.[10] or Szilagyi et al.[11] There are several factors which have contributed to this rate of primary graft failure. Thirty-seven per cent of our patients who required secondary vascular reconstruction had documented diabetes mellitus, and we have previously reported poor patency rates following aortobifemoral bypass grafting in this group of patients.[7,8] Neither Najafi nor Szilagyi comment on how many of their patients had diabetes mellitus or how diabetes affected patency after secondary reconstruction in their series. In addition, this report spans twelve years, and during the early part of our series the significance of minimal profunda femoris lesions was not appreciated. Many lesions of the profunda femoris which now would be reconstructed primarily were not initially repaired. These patients ultimately experienced graft thrombosis and later returned for repair which included secondary profunda femoris reconstruction. Finally, until four years ago, all profunda femoris lesions were routinely patched with Dacron. As this report has demonstrated, Dacron is associated with poorer long-term patency than autogenous profunda femoris reconstructions, and since we started using autogenous profunda femoris and reconstructive techniques with the primary operation we have seen few secondary reconstruction failures.

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Cancer Risk in Extensive Ulcerative Colitis

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Two hundred thirty-four patients with extensive ulcerative colitis from the city of Göteborg, Sweden have been followed up and the cumulative risk of development of cancer of the large bowel was estimated. These patients constitute all persons in this region who developed an extensive ulcerative colitis between 1951 and 1974. All patients were followed up until December 1975. The mean observation time was 8.5 years, median value six years. Fifteen patients developed carcinoma of the large bowel. Five of the 15 patients were still alive in December 1975. The expected number of colorectal carcinomas in a matched reference group was 0.49. The cumulative incidence of carcinoma 25 years after the onset of colitis for the whole group of patients was 34% and for those who developed the disease before 25 years of age it was 43%.

PATIENTS WITH EXTENSIVE ulcerative colitis run a greater risk of developing carcinoma of the large bowel than the general population. Opinions as to how large this risk is differ greatly between different authors.[1,2,5,6] This is hardly surprising however, as there have been differences in the method of collection of materials and the duration of the colitis has not always been taken into account, as has recently been pointed out by Devroede and Taylor.[7]

The poor prognosis in patients with UC and cancer of the large bowel makes it highly important to identify and treat patients at high risk in time.[14] Accurate knowledge of the cancer risk in this group of patients is therefore necessary. There is now convincing evidence that the colitis patients most susceptible to malignant changes are those with radiological involvement of the large bowel to at least the right flexure.[6,8,17] There are only few reports of large bowel carcinoma in which the inflammatory bowel disease has been localized exclusively to the rectum or the left side of the colon.[4,8,10,17,18] For the sake of clarity, it is therefore important to define the extension of the disease in the large bowel when the incidence of carcinoma in UC is investigated. This incidence must be quite different when all cases of UC are included in a series and when the incidence is calculated on groups of patients with the same extension of the disease.

Apart from the extension of the disease in the large bowel, the duration of the colitis in the individual patient is a most important factor for evaluating the cancer risk. Remarkably little attention has been paid to the variation in the duration of the disease between different patients when the incidence of cancer in UC has been calculated. In published reports the crude incidence has usually been used.[1,11,19] However, the use of the crude incidence to evaluate the risk of carcinoma in UC is misleading as it fails to correct for differences in duration between individual patients. The figures may thus underestimate the true incidence of carcinoma in UC. The time factor is essential and by employing the life table concept much more sophisticated and accurate results can be obtained.[6,7]

The aim of the present investigation has been to calculate the cumulative incidence of carcinoma in patients from a well-defined area of Sweden with extensive colitis *i.e.* radiological involvement of the large bowel to at least the right flexure.

Material and Methods

Hospital records for the population of Göteborg and listing of diagnosis of any type of inflammatory large bowel disease recorded during 1951–1974 were collected and examined. Only records from patients who were resident in the city of Göteborg were included in the study. Ulcerative colitis was defined by the usual clinical criteria and supported by radiological and sigmoidoscopic findings. Moreover, the diagnosis was supported by histological examination of the surgical specimen, rectal biopsy or postmortem investigation in the vast majority of patients. Patients with Crohn's colitis were excluded. Extensive colitis was defined as rectal involvement as shown by sigmoidoscopy and

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Submitted for publication: March 25, 1977.

0003-4932/78/1200/0824 $00.75 © J. B. Lippincott Company

TABLE 1. *Carcinoma of the Large Bowel in Association with Extensive Ulcerative Colitis According to the Length of History in the Number of Duration Years of Follow-up**

	D_i	C_i	$\lambda = C_i/D_i$	$P_i = e^{-\lambda \cdot t}$	$Q_i = 1 - P_i$	S.D.	P	Q	S.D.
1–5 years	875	0	0.000	1.000	0.000	0.000	1.000	0.000	0.000
6–10 years	523	3	0.006	0.970	0.030	0.017	0.970	0.030	0.017
11–15 years	282	4	0.014	0.932	0.068	0.032	0.904	0.096	0.035
16–20 years	147	5	0.035	0.839	0.161	0.066	0.758	0.242	0.066
21–25 years	73	2	0.027	0.874	0.126	0.083	0.663	0.337	0.086

* One patient with 44 years duration is not included in the table.

radiological evidence of large bowel involvement extending at least to the right hepatic flexure. As the majority of previous investigations have defined extensive colitis in this way,[5,6] use of this definition makes comparison with earlier studies possible.

According to this definition 234 patients had ulcerative colitis with total involvement of the large bowel, and these cases constitute the material of this study. The outcome in all patients could be followed up until December 1975. 129 patients were women. 154 patients had undergone proctocolectomy or colon resection with ileorectal anastomosis. The mean observation time was 8.5 years, median value six years.

To determine the cumulative risk of large bowel carcinoma in a patient with total involvement of the colon the concept of duration–years was used. Patients began to contribute duration–years from the year after the onset of the disease. The difference between duration–years and patient–years, *i.e.* one complete year of follow-up of an individual patient, was in our material usually small as most of the patients came to the hospital shortly after the onset of the disease. Patients then contributed to the total number of duration–years until they underwent proctocolectomy, died or until the closing date of the study, December 31, 1975. Those patients who had a large bowel resection or an ileorectal anastomosis were considered to contribute duration–years until the remaining part of the colon was removed, the patient died or until December 31, 1975.

The duration–years have been divided into five year intervals. Thus, a patient who first presented his disease in 1951 and underwent a proctocolectomy in 1963 contributed 12 duration–years, which means that he contributed 5 + 5 + 2 years in the first, second and third five year period, respectively. The number of patients (six) with a duration of more than 25 years was too small for accurate calculations. The maximum number of five year periods was therefore 5 ($i = 1, 2, 3, 4, 5$).

The risk of developing carcinoma of the large bowel is assumed to change with time but these changes have been considered to be small within each 5-year period.

D_i is the total sum of all duration–years within each five year period and C_i the number of carcinomas in a particular five year period. The risk (λ) of developing carcinoma within the five year period is estimated from the ratio C_i/D_i.

The probability (P_i) of a patient who lived at the beginning of an interval *not* developing a carcinoma during the interval can be calculated from $P_i = e^{-\lambda \cdot t}$, where t is the time length of the interval. Consequently, the probability of developing a carcinoma (Q_i) in the same interval is $Q_i = 1 - P_i$.

The cumulative risk after a certain period of time of a patient not developing a carcinoma can be calculated as the product of the incidences during each five year interval. $\mathbf{P} = P_1 \cdot P_2$ --- P_5 and the cancer risk will consequently be $\mathbf{Q} = 1 - \mathbf{P}$.

Results

Fifteen patients with 17 large bowel carcinomas were found. Five in colon ascendens, five in transversum, three in sigmoid colon and four in rectum. Two of the patients with rectal carcinoma had a second cancer

TABLE 2. *Carcinomas of the Large Bowel in Association with Extensive Ulcerative Colitis According to the Length of History in the Number of Duration Years of Follow-up**

Debute ≤25 years	D_i	C_i	$\lambda = C_i/D_i$	$P_i = e^{-\lambda \cdot t}$	$Q_i = 1 - P_i$	S.D.	P	Q	S.D.
1–5 years	429	0	0.000	1.000	0.000	0.000	1.000	0.000	0.000
6–10 years	264	1	0.004	0.980	0.020	0.020	0.980	0.020	0.020
11–15 years	149	3	0.020	0.905	0.095	0.052	0.887	0.113	0.054
16–20 years	81	3	0.037	0.831	0.169	0.089	0.737	0.263	0.090
21–25 years	39	2	0.051	0.775	0.225	0.140	0.572	0.429	0.124

* Onset before 25 years of age.

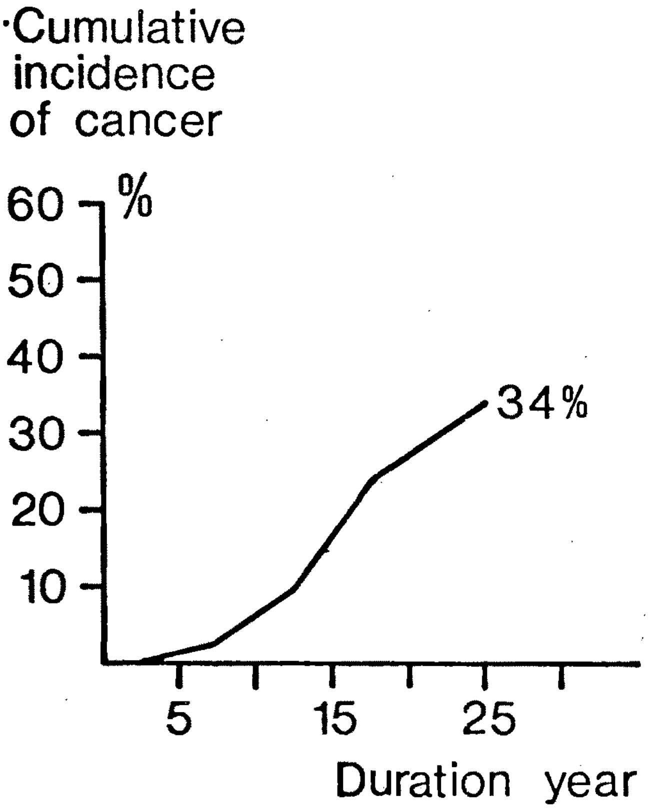

FIG. 1. Estimated cumulative probability of development of cancer in extensive ulcerative colitis.

in colon ascendens and transversum respectively. The mean age at the onset in these patients was 26 years. The duration of UC in these patients varied between seven and 44 years. The mean duration was 17 years. Five of the 15 patients were still alive in December 1975. The expected number of colorectal carcinoma in a matched reference group according to the Swedish Cancer Register is 0.49.

Table 1 shows the incidence of carcinoma in the whole group of patients. Figure 1 depicts the cumulative incidence of carcinoma in the whole group of 234 patients calculated by the actuarial material method from the data in Table 1. The cumulative incidence of developing a carcinoma 25 years after the onset of colitis symptoms was 34%. When the same calculation was performed on those patients, whose UC began before the age of 25 this figure rose to 43% (Fig. 2, Table 2). The difference in cancer incidence between the two groups after 25 years' duration was not significant.

Discussion

The results of the present study indicating that two out of five patients will eventually get a carcinoma are in accordance with those reported by deDombal[5] and Devroede et al.[6] In both these studies the incidence of carcinoma in patients suffering from extensive colitis were also studied by actuarial methods. Though the extensive colitis was carefully defined in these studies, the patients on which the result was based were not collected from a defined area but included all cases who attended the colitis clinics. Both series therefore might in fact represent a more or less selected group of patients, as compared with the present series which includes patients exclusively from the area of Göteborg. This difference is possibly the most important in explaining that the cancer incidence in these series is slightly higher than in the present investigation.

It has been suggested that the difference in incidence of carcinoma in UC might be due to geographical differences.[12] Thus, Nedbal et al.[19] reported a crude incidence of 0.5% in Czechoslovakia. Aktan et al.[1] from Turkey and Bonnevier et al.[2] from Denmark reported no large bowel carcinoma in 60 and 322 cases of UC, respectively. In the evaluation of the cancer risk none of these authors correlated the duration of the disease to the extension of the bowel involvement. As previously mentioned, it is far from satisfactory to treat

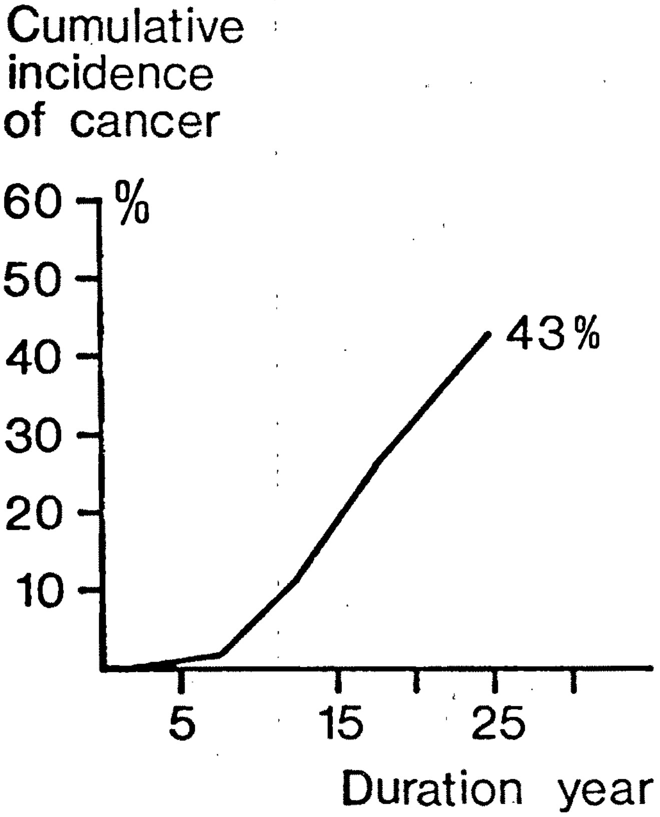

FIG. 2. Estimated cumulative probability of development of cancer in extensive ulcerative colitis. Onset before 25 years of age.

all patients with colitis of varying distribution as one big group and just calculate the crude incidence without taking into consideration the individual duration of the disease. A possible geographical difference in the incidence of carcinoma of the colon in UC still remains to be demonstrated.

Lennard-Jones et al.[16] are of the opinion that patients with quiescent extensive colitis can be managed conservatively provided that close and regular supervision can be guaranteed to the patient. This means life-long follow-up twice a year with sigmoideoscopy and rectal mucosal biopsy and a barium enema or colonoscopy if clinically indicated. They do not define this indication. If close follow-up is prevented by circumstances, they recommend elective surgery with proctocolectomy as the safest course. With a mean length of follow-up of 3.3 years they have found three patients with carcinoma of the large bowel, all alive seven, six and two years respectively after surgery. In these three cases epithelial dysplasia was observed on rectal mucosal biopsy. The future outcome of this interesting prospective investigation of patients with long-standing extensive UC will be most important. However, there seems to be accumulating evidence that rectal biopsy for precancer in ulcerative colitis is not 100% reliable.[9] In a recent group of patients with extensive UC referred to this hospital from other parts of Sweden, ten patients had the full picture of epithelial dysplasia in rectal biopsies. All these patients underwent proctocolectomy and in three of them a carcinoma was found. Another patient with carcinoma of the large bowel and UC had a negative rectal biopsy. The full picture of precancer in the rectal biopsy is to our mind an absolute indication for proctocolectomy. However, as a negative biopsy does not exclude a large bowel carcinoma, epithelial dysplasia in the rectal biopsy can so far not be regarded as the exclusive indication for surgery. Furthermore, examination of the large bowel by barium enema has in two of our cancer cases been disappointing. In one patient with UC there was a normal barium enema 16 months before a carcinoma of the large bowel was found of a later barium enema, and in another patient 14 months before the cancer was discovered. We therefore agree with the Leeds-group[5] that despite most careful follow-up of the patients, detection of a carcinoma cannot be guaranteed in patients with long-standing extensive ulcerative colitis. It is possible that regular colonoscopy of these patients with simultaneous multiple biopsies can be a useful tool for the identification of those patients who are especially prone to develop a carcinoma. However, this will only be possible in certain centres with an organized follow-up system, with a well-trained colonoscopist and with a pathologist, who is interested and skilled in interpreting large bowel biopsies. With the present-day level of knowledge, we believe that elective surgery for patients with extensive colitis of 10–15 years duration shall be carefully considered providing that the diagnosis of UC is clearly established.

The low incidence of carcinoma in the Danish series[2] was explained as a probable result of an active approach in the treatment of extensive colitis. A large number of their patients, who suffered from colitis in the entire colon as well as the majority of the patients showing a chronic continuous course of the disease were operated upon. They had no carcinoma of the large bowel in the whole material, which might be the result of a high frequency of proctocolectomy. A similar approach has been used in our hospital during the last few years. During the last five years we have had two carcinomas among the patients from the city of Göteborg. One patient presented with an ileus due to a carcinoma of the large bowel. As he was in excellent general health he had not been seen by a physician for 19 years. This patient illustrates the necessity of having complete control of *all* patients with UC. The responsibility for this control must lay with the physician. The other patient was operated upon with proctocolectomy due to a precancerous lesion in the rectal biopsy. A small carcinoma was found in the specimen. This cancer was not seen at a large bowel enema one and one-half months before surgery.

Life with an ileostomy is not so frightening that these patients should be exposed to a type of Russian roulette with about a 35% chance of getting a carcinoma after 25 years' duration of the disease. If the patient is provided with a continent ileostomy an active surgical approach to this group of patients seems to us even more justified as the quality of life for these patients is most encouraging.[25]

Acknowledgments

Statistical analyses have been performed in collaboration with Mr. A. Odén, Ph.D. and Mr. N. G. Pehrsson, Department of Mathematics, Chalmers University of Technology, Göteborg.

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STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION

Act of August 12, 1970: Section 3685. Title 39 United States Code)

Date of Filing—September 12, 1978

Title of Publication—Annals of Surgery

Frequency of Issue—Monthly

Location of Known Office of Publication—East Washington Square, Philadelphia, PA 19105

Location of the Headquarters or General Business Offices of the Publishers—East Washington Square, Philadelphia, PA 19105

Publisher—J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105

Editor—David C. Sabiston, Jr., M.D., Dept. Surgery, Duke Univ. Med. Center, Durham, NC 27710

Managing Editor—Peter Dechnik, East Washington Square, Philadelphia, PA 19105

Owner—J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105

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Annals of Surgery (ISSN 0003-4932) is published monthly for $27.00 per year for the United States and its possessions;
resident rate (U.S. only) $19.00; all other countries $37.00; by J. B. Lippincott Co., East Washington Square,
Philadelphia, PA 19105. Second class postage paid at Philadelphia, PA and at additional mailing offices.
POSTMASTER: Send address changes to Annals of Surgery, J. B. Lippincott Co.,
East Washington Square, Philadelphia, PA.
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VOL. 188 JULY-DECEMBER 1978

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
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[Amikacin] also has the remarkable
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ne aminoglycoside-inactivating enzyme.”

w MD, An Overview of Pediatric Experience with
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ncountered additional
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“Amikacin sulfate...should be
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with serious sepsis

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“All isolates were inhibited by amikacin and
95% were killed by concentrations achievable
in serum with recommended doses

Leonard JM, McGee ZA, Alford RH: Gentamicin-resistant bacillary infectio
Arch Intern Med 138:201-205, Feb. 197

“All serum levels obtained within three hour
following a dose of amikacin exceeded the
MIC’s of the infecting organisms..

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237:562-564, Feb. 197

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and gentamicin. *N Engl J Med* 296:349-353, Feb. 197

“...amikacin provides the physicia
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in question

Klainer AS, Five questions: A comparativ
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film Sept. 197

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four, netilmicin

Price K, et al: Amikacin activity. *Am J Me*
(special issue) 14-24 June 1977

Can any hospital antibiotic be this good?

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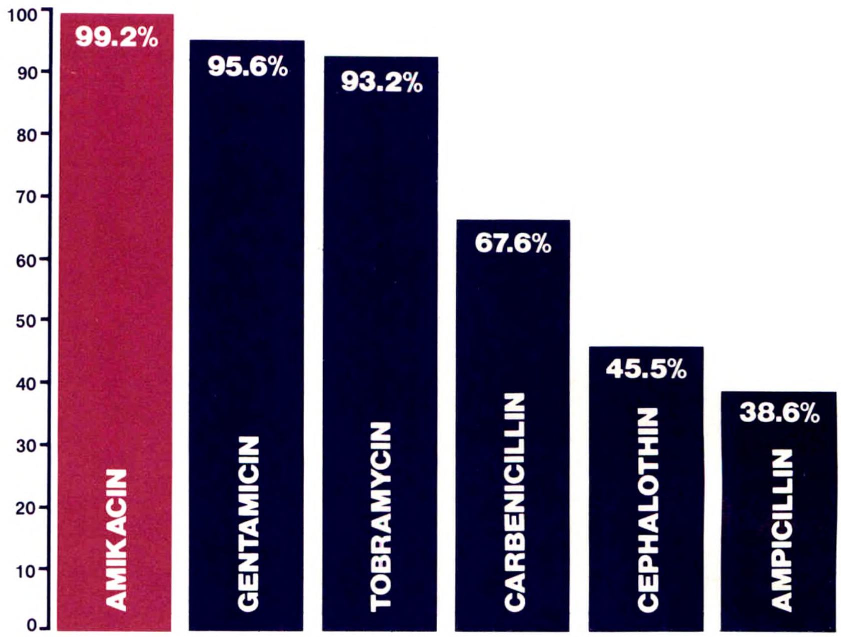
In-vitro superiority against today's gram-negative hospital pathogens*

Against 409 bacterial isolates, Amikin® (amikacin sulfate) activity was compared to leading injectable antibiotics. *None* of these agents inhibited as high a percentage of strains as did Amikin.

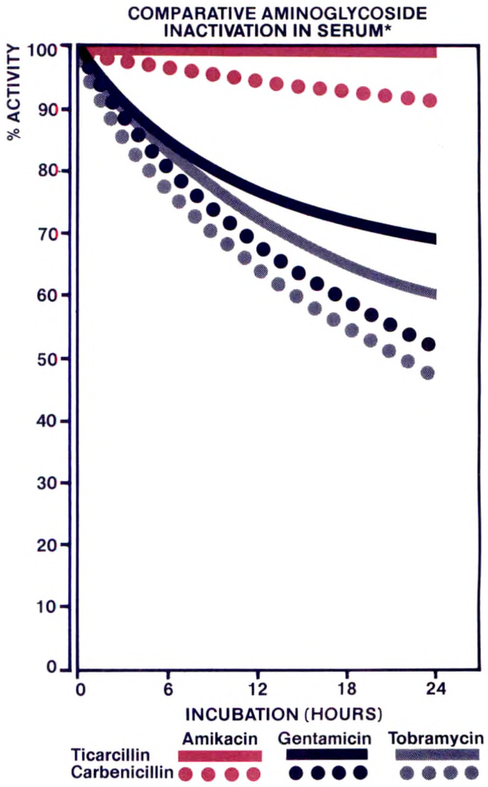
Susceptibility determined by the agar dilution test method, data on file, Bristol Laboratories. *Caution, *in vitro* data cannot be directly correlated to clinical effectiveness.



Least inactivated in combination

When carbenicillin or ticarcillin is combined *in vitro* with ordinary aminoglycosides, a significant reduction in aminoglycoside activity may occur. Virtually unaffected in the presence of ticarcillin, Amikin is also minimally compromised by carbenicillin...while other aminoglycosides may lose up to 50% of their activity.

Adapted from Holt HA, Broughall JM, McCarthy M, et al: Interactions between aminoglycoside antibiotics and carbenicillin or ticarcillin, *Infection* 4(2):107-109, 1976.
*Caution, *in vitro* data cannot be directly correlated to clinical effectiveness.



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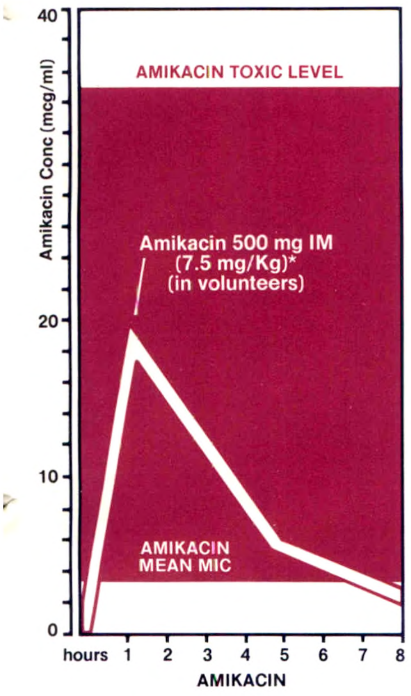
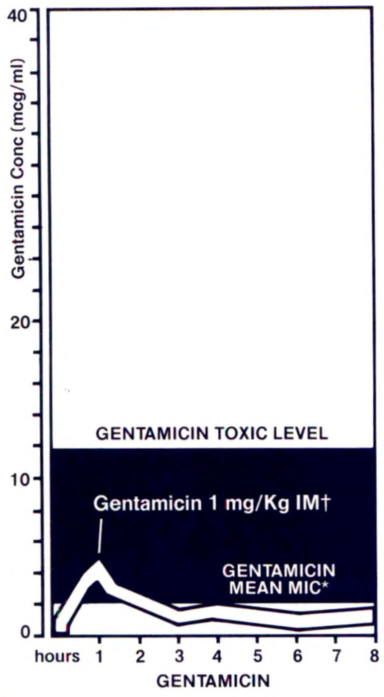




Broader therapeutic index

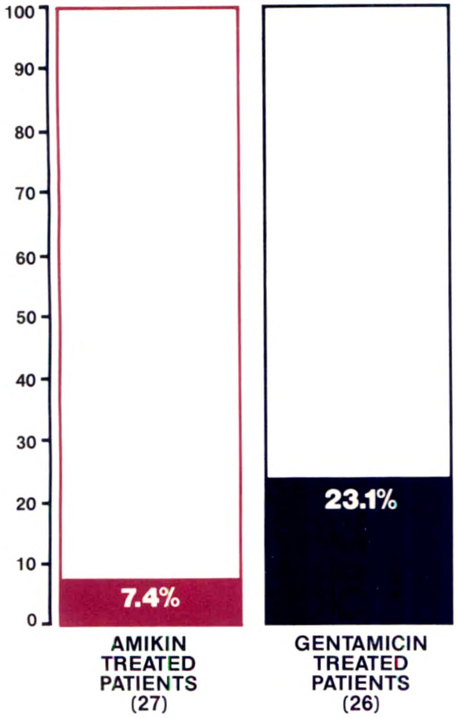
Amikin's Toxic-to-Therapeutic Index (ratio of toxic serum level to Mean MIC) is three times greater than the next leading aminoglycoside!

Because individual patient serum levels may vary from statistical averages, Amikin's broader margins reduce the risk of subtherapeutic or toxic dosage.

* Data on file, Bristol Laboratories

†Concentration curves adapted from: Winter RE, Litwack KD, Hewitt WL: *J infect Dis* 124 (suppl): 590-595, December 1971

COMPARISON OF OTO- AND NEPHROTOXICITY IN ONE STUDY AS DETECTED BY AUDIOMETRIC & RENAL FUNCTION MONITORING



Well tolerated

As with other aminoglycosides, adverse auditory and renal reactions may occur at higher doses, reversible in some instances. But, in a study comparing the oto- and nephrotoxicity of amikacin and gentamicin among 53 monitored patients, Amikin demonstrated a significantly reduced side effects risk. (Other published studies have shown little or no differences in toxicity).

Special Note: In Amikin clinical trials, hearing loss was rarely clinical and usually an audiogram was needed to identify such a loss. Adverse renal reactions due to Amikin usually consisted of elevations of serum creatinine and/or BUN, which were usually reversible.

Adapted from Lerner SA, Seligsohn R, and Matz GJ. Comparative clinical studies of ototoxicity and nephrotoxicity of amikacin and gentamicin. *Am J Med* (special issue): 113-117, June 1977.

Probably today's most important hospital antibiotic.

Please see brief summary of prescribing information following.

AMIKIN® IM IV
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Probably today's most important hospital antibiotic.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
AMIKIN® (amikacin sulfate)
For complete information, consult Official Package Circular. (1) AMIKIN 5/24/76

Warnings:
Patients treated with aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use.

Ototoxicity, both auditory and vestibular, can occur in patients treated at higher doses or for periods longer than those recommended. The risk of amikacin-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing.

The ototoxicity potential of amikacin in infants is not known. Until more safety reports become available, amikacin should be used in infants only in those specific circumstances when susceptibility testing indicates that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed closely for evidence of toxicity.

Aminoglycosides are potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Evidence of impairment in renal, vestibular or auditory function requires discontinuation of the drug or dosage adjustment.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 35 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells and casts.

Concurrent and/or sequential use of topically or systemically neurotoxic or nephrotoxic antibiotics should be avoided.

Amikin should not be given concurrently with potent diuretics.

Usage in Pregnancy: Amikin should be used in pregnant women only when clearly needed.

Indications:
Serious infections due to susceptible strains of Gram-negative bacteria including pseudomonas sp., *E. coli*, indole-positive and indole-negative proteus sp., providencia sp., klebsiella-enterobacter-serratia sp., and acinetobacter sp. Culture and sensitivity studies should be performed.

Clinical studies have shown Amikin to be effective in bacteremia and septicemia (including neonatal sepsis); in serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft-tissue; intra-abdominal infections (including peritonitis); and in burns and post-operative infections (including post-vascular surgery). Clinical studies have shown Amikin (amikacin sulfate) also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Amikin injectable, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

Bacteriologic studies should be performed to identify causative organisms and their susceptibilities to amikacin. Amikin may be considered as initial therapy in suspected Gram-negative infections and therapy may be instituted before obtaining the results of susceptibility testing. Clinical trials demonstrated that Amikin was effective in infections caused by gentamicin and/or tobramycin resistant strains of Gram-negative organisms, particularly *Proteus rettgeri, Providencia stuartii, Serratia marcescens* and *Pseudomonas aeruginosa*. The decision to continue therapy with the drug should be based on results of the susceptibility tests, the severity of the infection, the response of the patient and the important additional considerations contained in the "Warning" box above.

Amikin has also been shown to be effective in staphylococcal infections and may be considered as initial therapy under certain conditions in the treatment of known or suspected staphylococcal disease such as, severe infections where the causative organism may be either a Gram-negative bacterium or a staphylococcus, infections due to susceptible strains of staphylococci in patients allergic to other antibiotics, and in mixed staphylococcal/Gram-negative infections.

Amikacin may be indicated in the treatment of neonatal sepsis when susceptibility testing indicates that other aminoglycosides cannot be used. In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin-type drug may be indicated because of the possibility of infections due to Gram-positive organisms such as streptococci or pneumococci.

Contraindications:
A history of hypersensitivity to amikacin.

Warnings:
See "Warning" box above.

Precautions:
Amikin is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymycin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Adverse Reactions:
Ototoxicity—See "Warning" box.

Nephrotoxicity—Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other—Skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

Dosage and Administration:
The usual I.M. or I.V. dose with normal renal function is 15 mg./Kg./day divided into 2 or 3 equal doses administered at equally-divided intervals. For the heavier individual (greater than 100 Kg.), the total daily dose should not exceed 1.5 Gms. per day.

When amikacin is indicated in newborns (see box "Warning"), it is recommended that a loading dose of 10 mg./Kg. be administered initially to be followed with 7.5 mg./Kg. every 12 hours.

The usual duration of treatment is 7 to 10 days. The total daily dose by all routes of administration should not exceed 15 mg./Kg./day for the average-weight person. In the unusual circumstances where treatment beyond 10 days is considered, the use of Amikin should be reevaluated and, if continued, renal and auditory functions should be monitored daily.

For patients with impaired renal function, whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval.

The solution for intravenous use is prepared by adding the contents of a 500 mg. vial to 200 ml. of sterile diluent such as Normal Saline or 5% Dextrose in Water or any other compatible solution.

The solution is administered over a 30- to 60-minute period.

Supplied:
Rubber-capped vials as a ready-to-use sterile aqueous solution: 100-mg., 500-mg., and 1.0-Gm. vials.

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Tablets

Percodan® Ⓒ II

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

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1. Determine need What is causing pain? How is it perceived by you and your patient?

2. Prescribe a rapid-acting agent Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.

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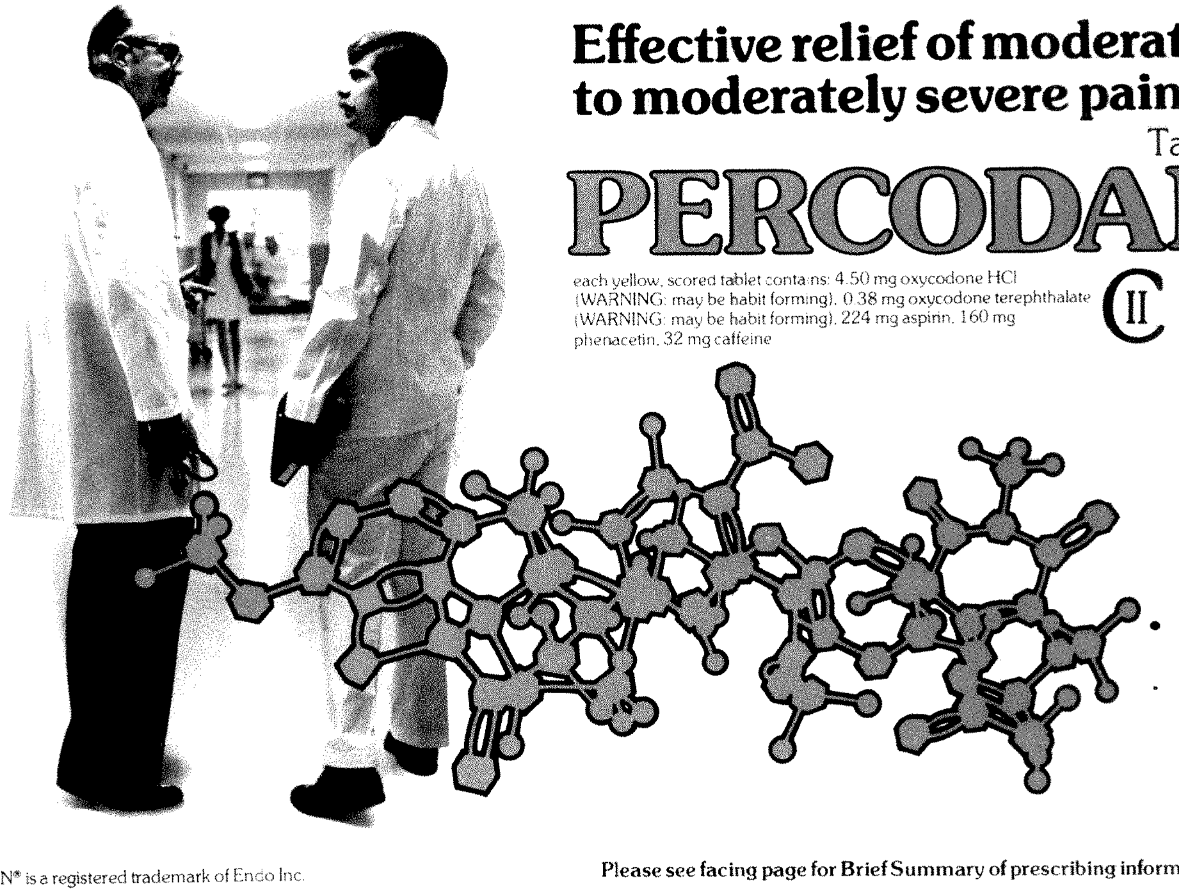
Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.

4. Provide adequate analgesia with minimum doses Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



Effective relief of moderate to moderately severe pain

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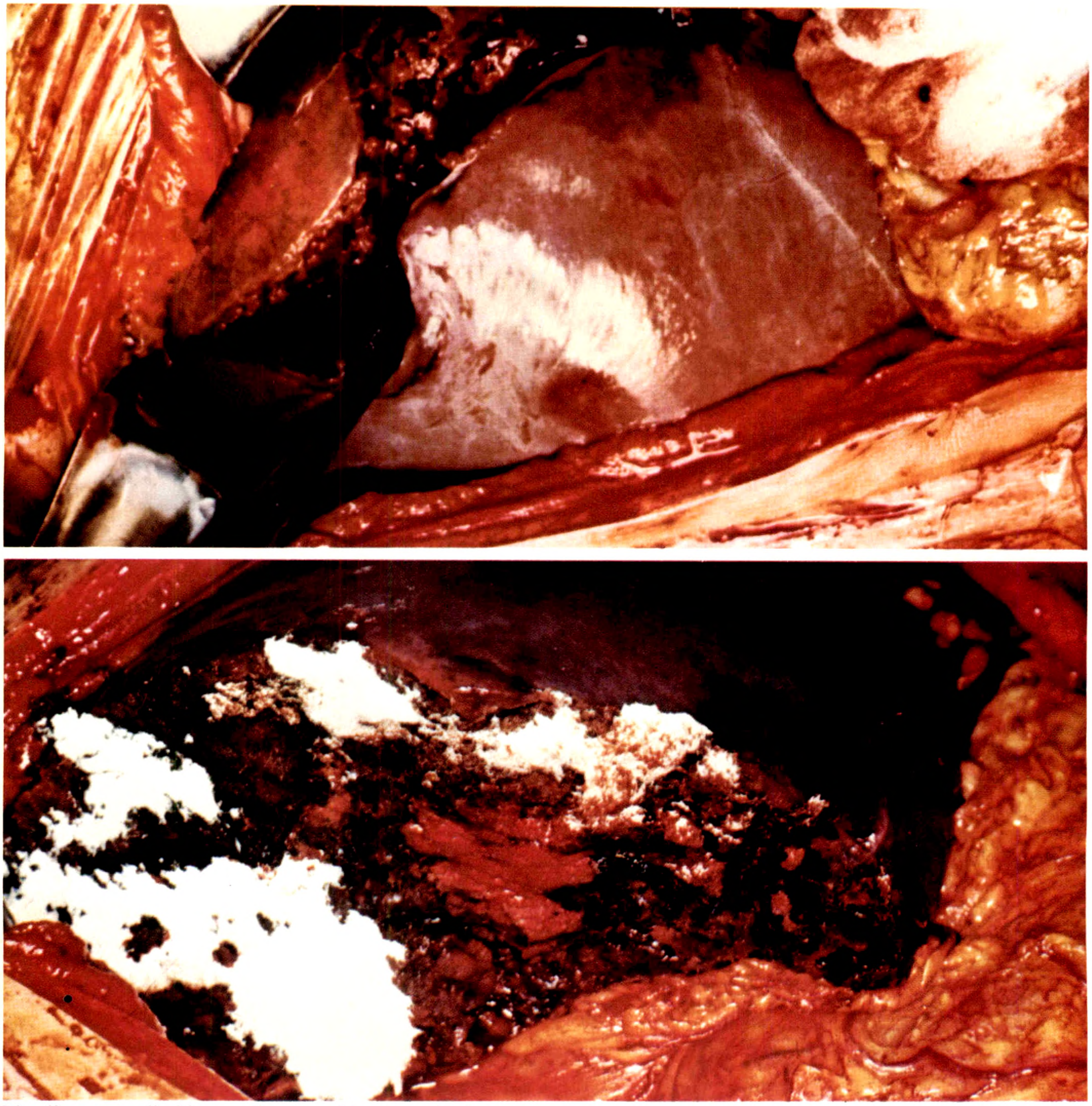
Please see facing page for Brief Summary of prescribing information

Avitene® (MCH) at work: hemostasis of stellate fracture of the liver



Bleeding controlled by application of hemostatic clamps; mattress sutures were then installed to secure hemostasis of major bleeders. Avitene was applied to control residual hemorrhage after removal of clamps.

Please see facing page for brief summary.

Avitene®

Microfibrillar Collagen Hemostat

Avitene® (microfibrillar collagen hemostat), derived from purified bovine corium, differs physically, chemically, and clinically from other topical hemostats. Supplementing conventional hemostatic techniques, Avitene extends your range of options when surgical bleeding problems are encountered. In cases where sutures, cautery, or pressure are impractical or ineffective, Avitene...

...a modified natural collagen, triggers the normal hemostatic mechanism, and produces a normal (physiologic) clot

...adheres tenaciously, even to irregular bleeding surfaces

...controls generalized bleeding from soft, friable tissues and highly vascularized organs

...produces minimal foreign body response

...is effective in most patients receiving heparin or aspirin, and in those who are moderately thrombocytopenic.

Numerous clinical studies document the efficacy of Avitene in a wide range of surgical procedures. Reprints of these studies and films showing surgeons using Avitene (microfibrillar collagen hemostat) are available at your request. Films currently available include: **(1)** Six Demonstrations of Effectiveness; **(2)** Use in Partial Nephrectomy; **(3)** Use in Thoracic Surgery; **(4)** Use in Neurosurgery; and **(5)** Use in Bone Bleeding.

For further information, write:
Medical Director, Avicon, Inc., P.O. Box 85,
Fort Worth, Texas 76101.

AVICON Avitene® is distributed by
Alcon Laboratories, Inc.

HOW TO USE AVITENE®

Keep Avitene dry. Care must be taken to ensure that Avitene is kept scrupulously dry, as prolonged exposure to moisture will impair its hemostatic efficacy. It will adhere to any wet surface and should be applied only with dry smooth forceps.

Apply Avitene directly to the source of the bleeding. It is important that Avitene be applied directly to the source of bleeding. Otherwise Avitene may seal over the exit site of deeper hemorrhage and conceal an underlying hematoma. Surfaces to be treated should first be compressed with dry sponges, and then covered with Avitene. The amount required will depend on the force and severity of the bleeding.

Apply pressure with a dry sponge. It is then necessary to apply moderate pressure over the Avitene with a dry sponge. The period of time necessary will vary with the severity of the bleeding, and may range from a minute for capillary bleeding, to three to five minutes for brisk bleeding or arterial leaks. For control of oozing from cancellous bone, Avitene should be firmly packed into the spongy bone surface.

Remove excess Avitene. After five to ten minutes, excess Avitene should be teased away; this can usually be accomplished without initiating rebleeding. If breakthrough bleeding occurs in areas of thin application, additional Avitene may be applied. The amount required depends, again, on the severity of bleeding. In capillary bleeding, one gram will usually be sufficient for a 50 cm^2 area. Thicker coverage may be required for brisk bleeding.

Avitene® (microfibrillar collagen hemostat)

Description: Avitene is an absorbable topical hemostatic agent prepared as a dry, sterile, fibrous, water insoluble partial hydrochloric acid salt of purified bovine corium collagen.

Indications: Avitene is used in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

Contraindications: Avitene should not be used in the closure of skin incisions as it may interfere with the healing of the skin edges.

Warnings: Avitene is inactivated by autoclaving. Ethylene oxide reacts with bound hydrochloric acid to form ethylene chlorohydrin. This product should not be resterilized. It is not for injection. Moistening Avitene or wetting with saline or thrombin impairs its hemostatic efficacy. It should be used dry. Discard any unused portion. As with any foreign substance, use in contaminated wounds may enhance infection.

Precautions: Only that amount of Avitene necessary to produce hemostasis should be used. After several minutes, excess material should be removed; this is usually possible without the re-initiation of active bleeding. Avitene contains a low, but detectable, level of intercalated bovine serum protein which reacts immunologically as does beef serum albumin. Increases in anti-BSA titer have been observed following treatment with Avitene. About two-thirds of individuals exhibit antibody titers because of ingestion of food products of bovine origin. Intradermal skin tests have occasionally shown a weak positive reaction to BSA or Avitene but these have not been correlated with IgG titers to BSA. Tests have failed to demonstrate clinically significant elicitation of antibodies of the IgE class against BSA following Avitene therapy. Care should be exercised to avoid spillage on nonbleeding surfaces, particularly in abdominal or thoracic viscera. Teratology studies in rats and rabbits have revealed no harm to the animal fetus. There are no well-controlled studies in pregnant women; therefore, Avitene should be used in pregnant women only when clearly needed.

Adverse reactions: The most serious adverse reactions reported which may be related to the use of this drug are potentiation of infection including abscess formation, hematoma, wound dehiscence, mediastinitis. Other reported adverse reactions possibly drug related are adhesion formation, allergic reaction, foreign body reaction, subgaleal seroma (report of a single case).

How supplied: In 1 g and 5 g sterile jars of sterile microfibrillar collagen hemostat all contained in sealed can. Sterility of the jar's exterior cannot be guaranteed if can seal is broken. Content of jar is sterile until opened.

6/78

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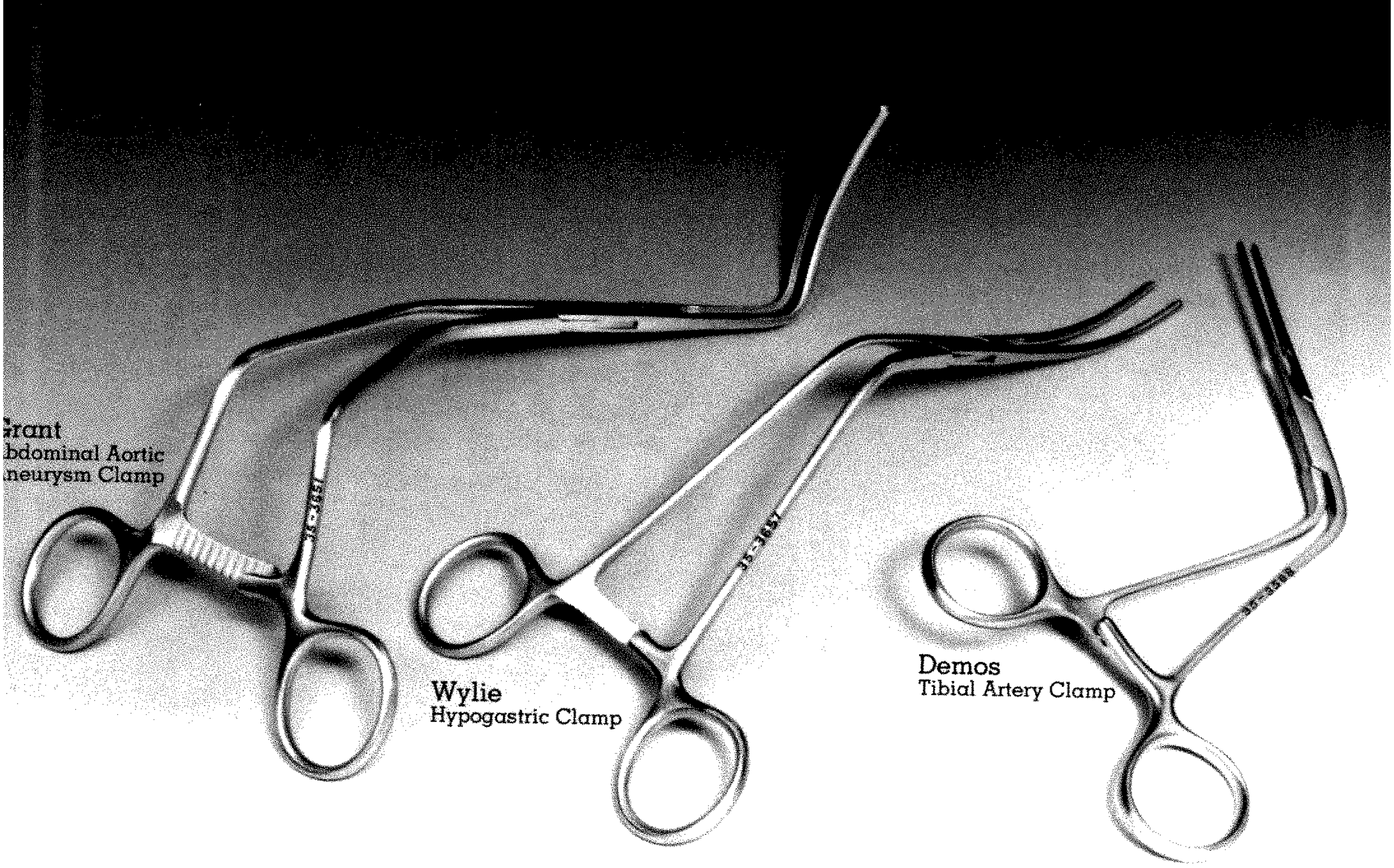

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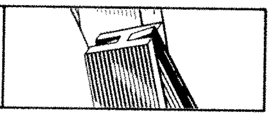
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Which type of duodenal ulcer patient benefits most from 'Tagamet'?

- ☐ newly diagnosed patients
- ☐ duodenal ulcer repeaters
- ☐ refractory patients
- ☐ hospitalized patients
- ☑ all of the above

Tagamet®

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cimetidine

Tablets, 300 mg. Injection, 300 mg./2 ml.

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Provides effective symptom relief, day and night

"Patients taking cimetidine showed a rapid increase in the number of pain-free days, and this number was significantly different from that in the placebo group in all treatment weeks....A similar trend was seen with respect to pain-free nights.[1]"

(From a double-blind study in 33 patients who received 'Tagamet' 300 mg. q.i.d. and 34 who received placebo, for six weeks.)

"Symptomatic improvement in patients given cimetidine was usually marked and occurred early...significant clinical improvement occurred in cimetidine-treated patients compared with placebo, as judged by the patients themselves and by the numbers of patients who became symptom-free during treatment.[2]"

(From a double-blind study in 65 duodenal ulcer patients who received 'Tagamet' 1 or 1.2 Gm./day and 24 who received placebo, for four weeks.)

1. Hetzel, D.J., et al.: Cimetidine in the treatment of duodenal ulcer. M.J. Australia 1:317-319 (Mar. 5) 1977.
2. Bardhan, K.D., et al.: The effect of cimetidine on duodenal ulceration: An interim report of a multicenter double-blind trial. Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists. Excerpta Medica, pp. 260-271, 1977.
3. Gray, G.R., et al.: Oral cimetidine in severe duodenal ulceration. Lancet 1(8001): 4-7 (Jan. 1) 1977.

newly diagnosed patients

duodenal ulcer repeaters

# of Duod[illegible]l Ulc[illegible]r [illegible]ati[illegible]nts

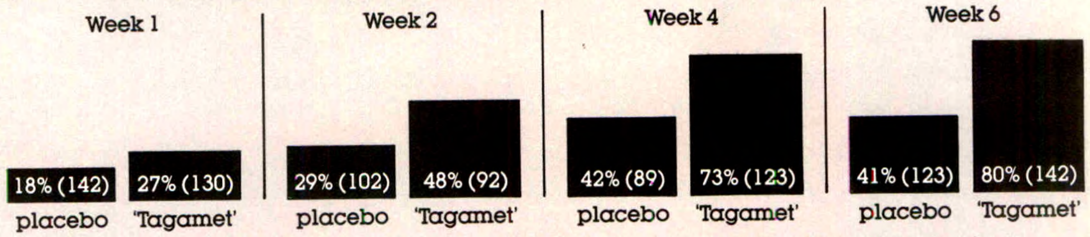
And promotes rapid ulcer healing

"After twenty-eight days, 17 of 20 (85%) patients receiving cimetidine showed ulcer healing, compared with 5 of 20 patients receiving placebo ($P < 0.0005$).[3]"

"Forty-seven (72%) of 65 patients treated with cimetidine had healed ulcers compared with 7 (29%) receiving placebo.[2]"

"This study demonstrates that ulcers of patients treated with cimetidine (1.2 g./day) have a significantly higher healing rate (82%) than those of patients receiving placebo (39%).[1]"

Incidence of Duodenal Ulcer Healing* Relative to Duration of Treatment[4]
(Numbers in parentheses are numbers of patients analyzed)



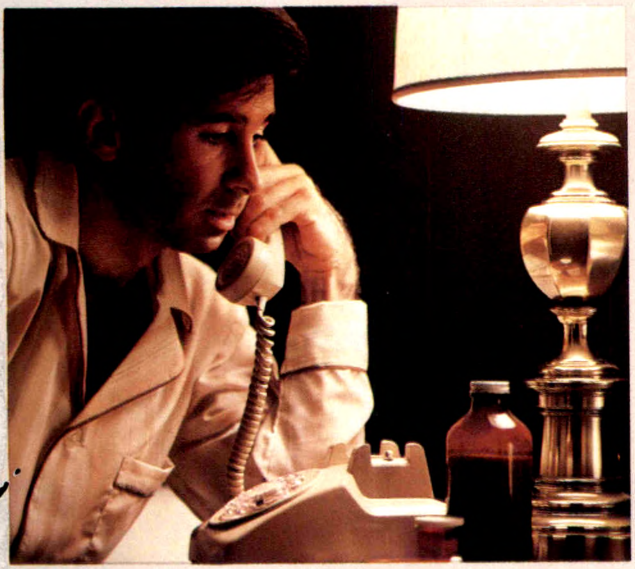
Daily dosage ranged from 0.8 to 2.0 Gm; five of the studies used 1.2 Gm./day. All patients were permitted p.r.n. antacids for relief of pain.

*In all studies, both presence of ulcer and ulcer healing were endoscopically confirmed.

4. Data from eight double-blind studies summarized by Winship, D.H.: Cimetidine in the treatment of duodenal ulcer. Review and commentary. Gastroenterology 74:402-406 (Feb.) 1978.

Please see following page for a brief summary of prescribing information.

refractory patients



hospitalized patients

Tagamet® brand of **cimetidine**

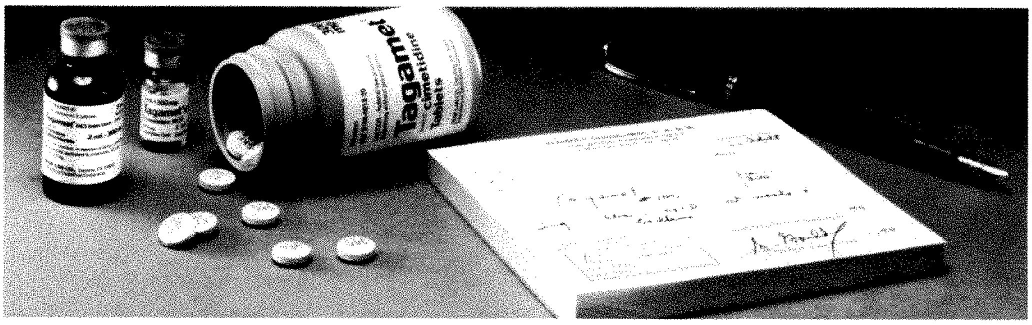
Tablets, 300 mg. Injection, 300 mg./2 ml.

For all of your duodenal ulcer patients

- Effective symptom relief, day and night

- Rapid ulcer healing

- Well tolerated



Dosage in Duodenal Ulcer

The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility. Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of child-bearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of reversible fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials and in 8 ml. multiple-dose vials in packages of 10.

Date of issuance Oct. 1978

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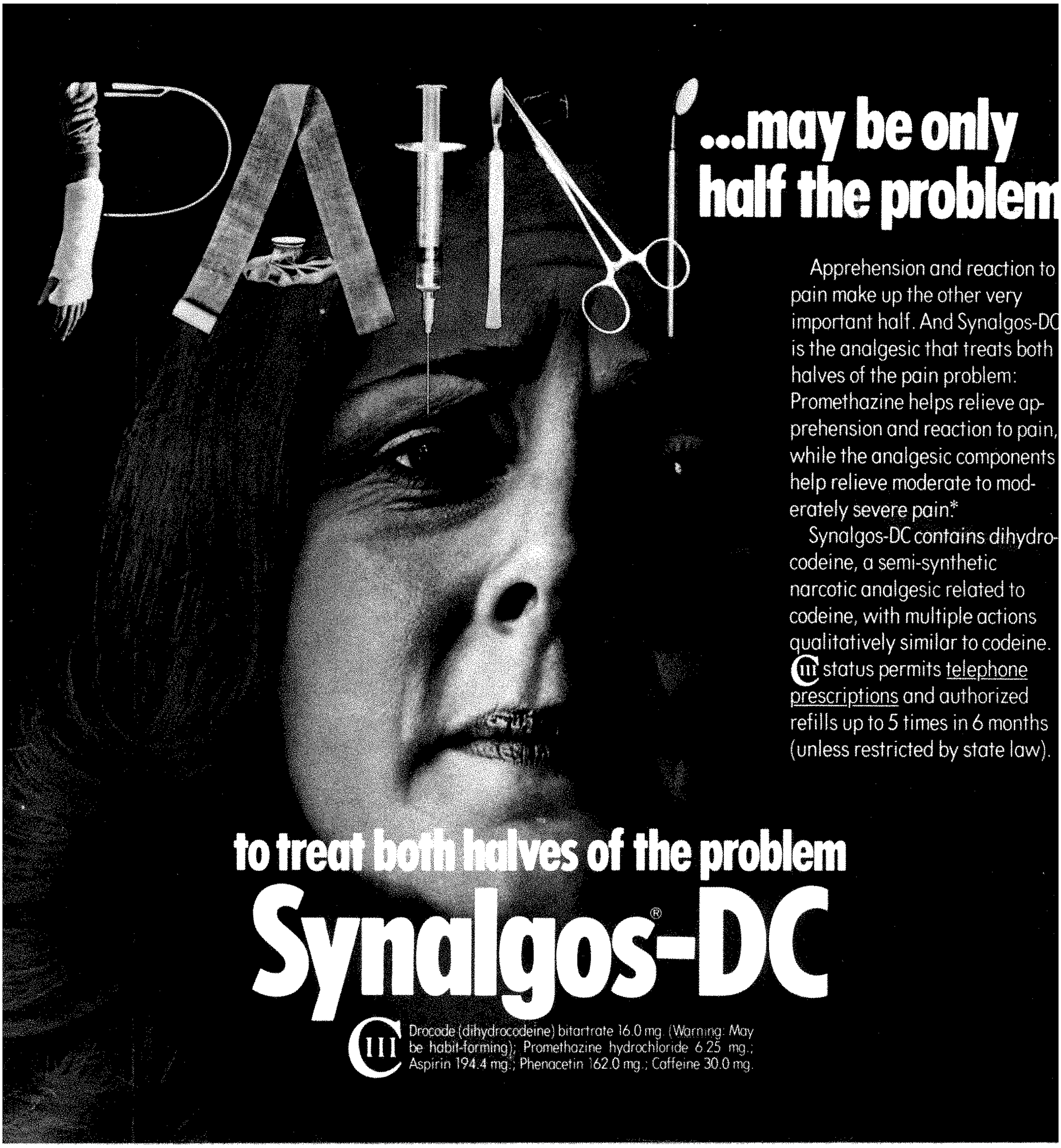

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Synalgos-DC contains dihydrocodeine, a semi-synthetic narcotic analgesic related to codeine, with multiple actions qualitatively similar to codeine. CIII status permits telephone prescriptions and authorized refills up to 5 times in 6 months (unless restricted by state law).

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
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Warnings: Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities. **Drug Dependence:** Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.
Like other narcotic-containing medications, dihydrocodeine is subject to the provisions of the Federal Controlled Substances Act. **Usage in Ambulatory Patients:** Dihydrocodeine and promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Synalgos-DC should be cautioned accordingly. **Interactions with other Central Nervous System Depressants:** Patients receiving other narcotic analgesics, general anesthetics, other phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Synalgos-DC may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Patients who have demonstrated a hypersensitivity reaction (e.g. blood dyscrasia, jaundice) with a phenothiazine should not be re-exposed to any phenothiazine, including Synalgos-DC, unless in the judgment of the physician the potential benefits of the treatment outweigh the possible hazards. **Usage in Pregnancy:** Reproduction studies have not been performed in animals. There is no adequate information on whether this drug may affect fertility in human males and females or has a teratogenic potential or other adverse effect on the fetus. **Usage in Children:** Since there is no experience in children who have received this drug, safety and efficacy in children have not been established. **Precautions:** Phenacetin has been reported to damage kidneys when taken in large amounts for a long time. Promethazine should be administered cautiously to patients with cardiovascular or liver disease. Synalgos-DC should be given with caution to certain patients such as the elderly or debilitated, and those with hypothyroidism, Addison's disease and prostatic hypertrophy and urethal stricture. **Adverse Reactions:** The most frequently observed reactions include lightheadedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, skin reactions, and rarely, hypotension. **Drug Interactions:** The CNS depressant effects of Synalgos-DC may be additive with that of other CNS depressants. See Warnings. Aspirin may enhance the effects of anticoagulants and inhibit the uricosuric effects of uricosuric agents. Consult direction circular before prescribing.

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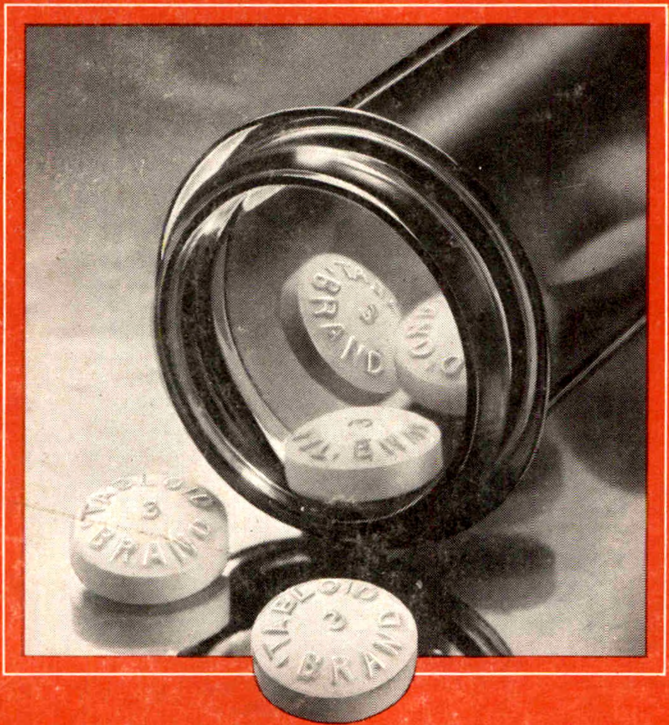

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